Scleroderma: oral mycophenolate

Evidence summary
Published: 29 July 2014
www.nice.org.uk/guidance/esuom32

Key points from the evidence

The content of this evidence summary was up-to-date in July 2014. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Observational studies suggest mycophenolate improves skin symptoms and may stabilise lung function in people with systemic sclerosis. The most common adverse effects were gastrointestinal tract disturbances and infections. However, observational studies have limitations and randomised controlled trials, particularly comparing mycophenolate with other treatments for scleroderma, are needed to clarify efficacy and safety in this condition.

Regulatory status: off-label. This topic was prioritised because there was a high volume of requests from the NHS. Immunosuppressants such as mycophenolate are widely used in people with scleroderma, but none are specifically licensed for this indication.
## Effectiveness

- Observational studies in people with diffuse cutaneous systemic sclerosis (n=25 to 147) suggest mycophenolate improves modified Rodnan skin scores by up to 10.0 points on a 51-point scale.

- Observational studies including people with systemic sclerosis-associated interstitial lung disease (n=20 to 125) suggest mycophenolate may stabilise lung function, based on disease-oriented outcomes, such as forced vital capacity percentage of the predicted normal value (FVC%).

- Most studies used mycophenolate mofetil, rather than mycophenolate sodium, at a dose of up to 1000 mg or 1500 mg twice daily.

## Safety

- Immunosuppressants including mycophenolate have been associated with increased risks of lymphomas, other malignancies, opportunistic infections that can be fatal, sepsis and neutropenia. ([mycophenolate mofetil](https://www.nice.org.uk) and [Myfortic](https://www.nice.org.uk) summaries of product characteristics [SPCs]).

- Mycophenolate has been associated with pure red cell aplasia and serious gastrointestinal adverse events ([mycophenolate mofetil](https://www.nice.org.uk) and [Myfortic](https://www.nice.org.uk) SPCs).

- The SPCs for mycophenolate mofetil state that there have been isolated reports of interstitial lung disease and pulmonary fibrosis in people treated with mycophenolate in combination with other immunosuppressants, some of which have been fatal.
Patient factors

- There is little evidence on the effect of mycophenolate on patient-oriented outcomes, such as functional ability or breathlessness.

- It is not known if mycophenolate has any effect on preventing scleroderma from progressing or on minimising any disability.

- In an observational study in people with diffuse cutaneous systemic sclerosis (n=109), mycophenolate was discontinued in 8% of people because of adverse effects. The most common adverse effects were gastrointestinal tract disturbances (4.6%) and infections (3.7%).

Resource implications

- The estimated annual cost of mycophenolate mofetil at a dose of 1000 mg twice daily is £345.14 (Drug Tariff June 2014; excluding VAT).

- The estimated annual cost of mycophenolate sodium (Myfortic) at a dose of 720 mg twice daily is £2353.40 (MIMS June 2014; excluding VAT).

Introduction and current guidance

Scleroderma is an autoimmune condition affecting the skin, internal organs and blood vessels. This causes scarring and thickening of the tissue in these areas. There are 2 main types of scleroderma: localised scleroderma, which affects just the skin; and systemic sclerosis, which may affect blood circulation and internal organs, as well as the skin.

The aim of treatment in scleroderma is to relieve symptoms, prevent the disease getting worse, detect and treat any complications and minimise disability through occupational therapy and physiotherapy. Because scleroderma can affect many different parts of the body, various different medications may be needed (NHS Choices: scleroderma).

Immunosuppressants such as methotrexate, cyclophosphamide and mycophenolate may be taken to suppress the immune system and attempt to slow the disease's progression. None of these drugs is licensed specifically for use in people with scleroderma and use of any of these drugs would be off-label (NHS Choices: scleroderma; Scleroderma Society: Understanding and Managing Scleroderma).

Evidence-based, consensus-derived recommendations for treating systemic sclerosis were
published by the European League against Rheumatism (EULAR) Scleroderma Trials and Research group in 2009 (Kowal-Bielecka et al. 2009). No formal recommendation on the use of mycophenolate was given because there was a lack of appropriate evidence. An update of the EULAR recommendations is expected in 2014.

Full text of introduction and current guidance.

**Product overview**

Mycophenolic acid is an immunosuppressant agent with antiproliferative activity that inhibits of the purine biosynthetic pathway. Mycophenolic acid is available as the prodrug mycophenolate mofetil or as mycophenolate sodium (Myfortic). Both mycophenolate products are licensed for the prophylaxis of acute transplant rejection. Neither is licensed for treating scleroderma, therefore use for this indication is off-label.

Full text of product overview.

**Evidence review**

There are no randomised controlled trials (RCTs) of mycophenolate for treating scleroderma. This evidence summary is therefore based on the largest, most recent observational studies that provide the best available evidence for using mycophenolate in people with this condition. Most people in the studies had diffuse cutaneous systemic sclerosis or systemic sclerosis-associated interstitial lung disease. Most studies used mycophenolate mofetil, rather than mycophenolate sodium, at a dose of up to 1000 mg or 1500 mg twice daily.

- A prospective, multicentre observational study in 147 people with early diffuse cutaneous systemic sclerosis assessed 5 different treatment protocols, 3 of which included mycophenolate mofetil (Herrick et al. 2010). In all patients, the modified Rodnan skin score decreased over time by a median of 8.5 points at 3 years (from a median of 24 [interquartile range 19 to 32] at baseline to 15.5 [interquartile range 9 to 24.5] on a 51-point scale). There were no statistically significant differences in the rate of change of skin scores over time between the different treatment protocols (p=0.43, or p=0.28 when adjusted for possible confounding factors).
A prospective, single-centre observational study assessed mycophenolate mofetil in 25 people with previously untreated recent-onset diffuse progressive cutaneous systemic sclerosis (Mendoza et al. 2012). The mean modified Rodnan skin score was reduced by 10 points, from 24.56±8.62 at baseline to 14.52±10.9 at an average of 18 months' follow-up (p=0.004). Lung function was assessed in 15 people using total lung capacity percentage of the predicted normal value (TLC%) and carbon monoxide diffusion capacity percentage of the predicted normal value (DLCO%). There was no change in either of these from baseline.

A retrospective, single-centre cohort study assessed mycophenolate mofetil in 98 people with diffuse cutaneous systemic sclerosis (Le et al. 2011). At 12-months' follow-up, there was a statistically significant reduction in the mean modified Rodnan skin score of 6.9 points; from a baseline of 24.4±9.5 to 17.5±10.4 (p<0.001). There was also a statistically significant improvement in physical disability assessed using the Health Assessment Questionnaire Disability Index (from a mean of 1.1±0.6 at baseline to 0.94±0.7 at 12 months; p<0.001), and no change in lung function (forced vital capacity percentage of the predicted normal value [FVC%] and DLCO%).

A systematic review and meta-analysis of observational studies assessed mycophenolate mofetil or mycophenolate sodium for the treatment of systemic sclerosis-associated interstitial lung disease (Tzouvelekis et al. 2012). This included a total of 69 people in 6 studies. The main efficacy outcome was lung function (FVC% and DLCO%), assessed before and at least 6 months after mycophenolate treatment. No statistically significant difference was seen for either outcome. For FVC%, the weighted mean difference was 1.48% (95% CI −2.77 to 5.72%, p=0.49), and for DLCO% it was −0.83% (95%CI −4.75 to 3.09%, p=0.93).

A retrospective, single-centre, case-control study compared mycophenolate mofetil or mycophenolate sodium (n=10) with oral or intravenous cyclophosphamide (n=10) in people with systemic sclerosis-associated interstitial lung disease (Panopoulos et al. 2013). There was no statistically significant change in lung function (as assessed by FVC%, DLCO% and TLC%) from baseline in either group. After 2 years of treatment, the difference from baseline in mean FVC% was 2.2±11.4% with mycophenolate (p=0.444) and 5.2±12.4% with cyclophosphamide (p=0.326).

A retrospective, single-centre, cohort study assessed mycophenolate mofetil in a wider population of 125 people with connective tissue disease-associated interstitial lung disease; 44 of whom had systemic sclerosis-associated interstitial lung disease (Fischer et al. 2013). For the entire cohort, mycophenolate mofetil was associated with statistically significant improvements in FVC% (7.3±2.6% at 156 weeks, p=0.004) and in DLCO% (7.1±2.8% at 104 weeks, p=0.01). The data presented in the paper for the subgroup of people with systemic sclerosis-associated interstitial lung disease were incomplete and difficult to analyse.
• A retrospective, single-centre, cohort study (Nihtyanova et al. 2007) assessed the tolerability of mycophenolate mofetil in 109 people with diffuse cutaneous systemic sclerosis. Most people (79%) had received the drug for at least 1 year, most commonly at a dose of 2000 mg daily. Mycophenolate mofetil was discontinued in 34% of people; in 8% because of adverse effects. Adverse reactions were reported in 12% of people, most commonly gastrointestinal tract disturbances (4.6%) and infections (3.7%).

• All the studies of mycophenolate for treating scleroderma are observational and, therefore, have limitations inherent in their non-randomised design. Most studies were single-arm, open-label studies, with no control group, in small numbers of people. This reduces the quality of the evidence on efficacy and safety that they can provide. The studies mainly reported disease-oriented outcomes such as skin score and lung function (FVC%, TLC% or DLCO%); defining what a clinically important difference is in these outcomes for people with scleroderma is difficult.

Full text of evidence review.

Context and estimated impact for the NHS

The estimated annual cost of mycophenolate mofetil at a dose of 1000 mg twice daily is £345.14 (Drug Tariff June 2014; excluding VAT). Mycophenolate sodium (Myfortic) is more expensive, at an estimated annual cost of £2353.40 for 720 mg twice daily (MIMS June 2014; excluding VAT).

No estimate of the current use of off-label mycophenolate for treating scleroderma in UK clinical practice was identified.

Full text of context and estimated impact for the NHS.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with scleroderma who are thinking about trying mycophenolate.
About this evidence summary

‘Evidence summaries: unlicensed or off-label medicines’ summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

Scleroderma is an autoimmune condition affecting the skin, internal organs and blood vessels. This causes scarring and thickening of the tissue in these areas. There are 2 main types of scleroderma: localised scleroderma, which affects just the skin; and systemic sclerosis, which may affect blood circulation and internal organs, as well as the skin (NHS Choices: scleroderma).

Localised scleroderma is the mildest form of scleroderma and can occur at any age. The disease is confined to the skin and underlying issues, causing one or more hard patches. Internal organs are not affected. Exactly how the skin is affected depends on the type of localised scleroderma. In morphoea, small oval skin patches appear anywhere on the body. The patches may fade after a few years and treatment may not be needed. In linear scleroderma, thickened skin occurs in lines across the face or scalp, leg or arm. Lines persist for longer than morphoea patches and can occasionally affect underlying bone and muscle (NHS Choices: scleroderma).

Systemic sclerosis can involve the skin, gastrointestinal tract (oesophagus, stomach and bowels), lungs, kidneys, heart and other internal organs. It can also affect blood vessels, muscles and joints. The tissues of involved organs become hard and fibrous, causing them to function less efficiently (Scleroderma Society: Understanding and Managing Scleroderma).

In people with systemic sclerosis, skin becomes puffy and thickens, which can restrict joint
movement. Facial skin also becomes tight, especially around the mouth. There are 2 types of systemic sclerosis: limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis. Limited cutaneous systemic sclerosis tends to progress more slowly than diffuse cutaneous disease, although it can be associated with complications such as pulmonary hypertension. It often starts as Raynaud's phenomenon, and other symptoms include thickening of the skin over the extremities and face, red spots (dilated blood vessels) on the skin and hard lumps of calcium underneath the skin (especially the fingertips). In diffuse cutaneous systemic sclerosis, skin changes can affect the whole body. Symptoms tend to come on suddenly and get worse quickly over the first few years; then the disease settles and skin may improve. If the gastrointestinal tract is affected, people with systemic sclerosis can have heartburn, diarrhoea, constipation or faecal incontinence. The heart, lungs or kidneys can be affected causing a range of symptoms such as shortness of breath, high blood pressure and pulmonary hypertension (NHS Choices: scleroderma).

The aim of treatment in scleroderma is to relieve symptoms, prevent the disease getting worse, detect and treat any complications and minimise disability through occupational therapy and physiotherapy. Because scleroderma can affect many different parts of the body, various different medications may be needed (NHS Choices: scleroderma).

Immunosuppressants such as methotrexate, cyclophosphamide and mycophenolate may be taken to suppress the immune system and attempt to slow the disease's progression. None of these drugs is licensed specifically for use in people with scleroderma and use of any of these drugs would be off-label (NHS Choices: scleroderma; Scleroderma Society: Understanding & Managing Scleroderma).

Evidence-based, consensus-derived recommendations for treating systemic sclerosis were published by the European League against Rheumatism (EULAR) Scleroderma Trials and Research group in 2009 (Kowal-Bielecka et al. 2009). With regard to immunosuppressants, these state the following:

- 2 randomised controlled trials (RCTs) have shown that methotrexate improves skin score in early diffuse systemic sclerosis. Positive effects on other organ manifestations have not been established. Methotrexate may be considered for treatment of skin manifestations of early diffuse systemic sclerosis.

- In view of the results from 2 high-quality RCTs and despite its known toxicity, cyclophosphamide should be considered for treatment of systemic sclerosis-associated interstitial lung disease.

No formal recommendation on the use of mycophenolate was given because there was a lack of
appropriate evidence. The report states that uncontrolled and retrospectively controlled studies with some immunosuppressive regimens (such as azathioprine, mycophenolate mofetil, and ciclosporin) have reported efficacy in selected manifestations of systemic sclerosis, but their efficacy has to be evaluated further in RCTs. An update of the EULAR recommendations is expected in 2014.

The British Society for Rheumatology is developing treatment guidelines for scleroderma, and consensus best practice recommendations for scleroderma are being developed by the UK Scleroderma Study Group.

Product overview

Drug action

Mycophenolic acid is an immunosuppressant agent with antiproliferative activity that inhibits the purine biosynthetic pathway. Mycophenolic acid is available as the prodrug mycophenolate mofetil or as mycophenolate sodium (Myfortic).

The summary of product characteristics for mycophenolate sodium (Myfortic, Novartis) states that mycophenolic acid (as sodium salt) and mycophenolate mofetil should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles.

Regulatory status

Mycophenolate mofetil is licensed in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. Mycophenolate sodium (Myfortic, Novartis) is licensed in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adults receiving allogeneic renal transplants.

Neither mycophenolate product is licensed for treating scleroderma, therefore using mycophenolate mofetil or mycophenolate sodium for this indication is off-label.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using mycophenolate mofetil or mycophenolate sodium outside their authorised indications.
Cost

Mycophenolate mofetil is £11.82 for 50×500 mg tablets (excluding VAT; cost taken from Drug Tariff, June 2014).

Mycophenolate sodium (Myfortic) is £96.72 for 120×180 mg tablets and £193.43 for 120×Myfortic 360 mg tablets (excluding VAT; costs taken from MIMS, June 2014).

Evidence review

There are no randomised controlled trials (RCTs) of mycophenolate for treating scleroderma. This evidence summary is therefore based on the largest, most recent observational studies that provide the best available evidence for using mycophenolate in people with this condition. Most people in the studies had systemic sclerosis (either diffuse cutaneous systemic sclerosis or systemic sclerosis-associated interstitial lung disease) and most studies used mycophenolate mofetil rather than mycophenolate sodium, at a dose of up to 1000 mg or 1500 mg twice daily.

Clinical effectiveness

Mycophenolate in diffuse cutaneous systemic sclerosis

Early diffuse cutaneous systemic sclerosis is associated with high morbidity and mortality. RCTs in people with this condition have been conducted with methotrexate, interferon-alpha, D-penicillamine and anti-transforming growth factor-β antibody therapy, but all have had disappointing results or shown limited efficacy (Herrick et al. 2010).

In 2010 a prospective, observational study estimated the relative effectiveness of different treatment approaches in early diffuse cutaneous systemic sclerosis, capturing entry and outcome data in a standardised way (Herrick et al. 2010). The study included 147 people who met American College of Rheumatology criteria for early diffuse cutaneous systemic sclerosis (within 3 years of the onset of skin thickening) from 11 UK centres and 1 non-UK centre. People could be treated according to 5 different protocols, 3 of which included mycophenolate mofetil, and were followed up for 3 years. The treatment protocols were as follows:

- intravenous cyclophosphamide 15 mg/kg monthly for 6 months followed by mycophenolate mofetil up to 1000 mg twice daily for 6 months (n=29)
- antithymocyte globulin 2.5 mg/kg daily for 5 days followed by mycophenolate mofetil up to 1000 mg twice daily for 11 months, starting 1 month after entry (n=25)
- mycophenolate mofetil up to 1000 mg twice daily for 12 months (n=61)
- no disease-modifying treatment (n=19)
- other immunosuppressant treatment (n=13).

The primary outcome was the modified Rodnan skin score, which is a measure of skin thickness. It has a maximum score of 51 (a score of 0 to 3 [0=uninvolved, 1=mildly thickened, 2=thickened, 3=severely thickened] is assessed at 17 body sites). The total skin score in all patients decreased over time from a median of 24 (interquartile range 19 to 32) at baseline to 15.5 (interquartile range 9 to 24.5) at 3 years; a fall of 8.5 points. There were no statistically significant differences in the rate of change of skin scores over time between any of the different treatment protocols, including the 'no disease-modifying treatment' protocol (p=0.43). However, patients were allowed to change protocols during the study. This study was not randomised and there were baseline differences between the groups. However, there was still no statistically significant difference between the different treatment protocols when the data was adjusted for possible confounding factors (p=0.28).

The authors of this study suggest their findings of an improvement in skin score of 8.5 points at 3 years are comparable to those of other studies. However, without head-to-head RCTs it is difficult to make comparisons.

A further prospective, observational study (European Scleroderma Observational Study) is ongoing in follow-up to the study published in 2010. This is comparing the effectiveness of 4 treatment protocols (mycophenolate mofetil, methotrexate, cyclophosphamide and 'no immunosuppressant treatment' in people with early diffuse cutaneous systemic sclerosis). The primary outcome is the modified Rodnan skin score.

A smaller prospective, single-centre, observational study (Mendoza et al. 2012) also found that mycophenolate improved skin scores. In 25 people with previously untreated recent-onset diffuse progressive cutaneous systemic sclerosis, a median dose of mycophenolate mofetil 2000 mg daily reduced the mean modified Rodnan skin score by 10 points; from 24.56±8.62 at baseline to 14.52±10.9 at an average of 18 months' follow-up (p=0.004). Lung function was also assessed in 15 people in this study, using total lung capacity percentage of the predicted normal value (TLC%) and carbon monoxide diffusion capacity percentage of the predicted normal value (DLCO%). There was no change in either of these; TLC% was 89.47±16.61% at baseline and 85.33±17.34% at the end of the study (p=0.13).

The authors suggest that the 10-point improvement in skin score seen with mycophenolate mofetil
is likely to be clinically significant in this population. However, defining what a **clinically important** difference in skin score is for people with scleroderma is difficult because of the limited evidence base. The authors also suggest that the reduction in skin score may be greater than that seen for other treatments, but without head-to-head RCTs, assessing comparative benefits is difficult. By way of some comparison, in the Scleroderma Lung Study (Tashkin et al. 2006; see below), which was an RCT that compared cyclophosphamide with placebo, a post-hoc analysis of 85 people with diffuse systemic sclerosis found a statistically significant difference in skin score between the groups of −3.06 (95% **confidence interval** [CI] −3.54 to −0.52; p=0.008), favouring cyclophosphamide.

A retrospective cohort study of mycophenolate mofetil for the treatment of diffuse cutaneous systemic sclerosis in a single, large tertiary centre was published in 2011 (Le et al. 2011). This included 98 people who were started on mycophenolate mofetil primarily for the treatment of active skin disease. Most people started treatment with mycophenolate mofetil 500 mg twice daily for 1 to 2 weeks, which was then titrated to a maximum dose of 1500 mg twice daily based on tolerance and response. At 12-months’ follow-up, there was a statistically significant reduction in the mean modified Rodnan skin score of 6.9 points, from a baseline of 24.4±9.5 to 17.5±10.4 (p<0.001).

This study also noted physical disability and lung function at baseline and at 12 months. Physical disability was assessed using the **Health Assessment Questionnaire Disability Index** (HAQ-DI), which has a score of 0 to 3. Scores of 0 to 1 generally represent mild to moderate difficulty, 1 to 2 represent moderate to severe disability, and 2 to 3 indicate severe to very severe disability. There was a statistically significant improvement in HAQ-DI from a mean of 1.1±0.6 at baseline to 0.94±0.7 at 12 months (p<0.001). Lung function was assessed by forced vital capacity percentage of the predicted normal value (FVC%) and DLCO%. There was no difference in either of these from baseline to 12 months; FVC% was 79.4±17.6% at baseline and 80.7±17.7% at 12 months (p=0.264).

**Mycophenolate in systemic sclerosis-associated interstitial lung disease**

Interstitial lung disease is one of the most common complications of systemic sclerosis and is associated with high morbidity and mortality. A multicentre, placebo-controlled RCT in 158 people found oral cyclophosphamide was of some benefit in people with systemic sclerosis-associated interstitial lung disease (Scleroderma Lung Study: Tashkin et al. 2006; see below). However, follow-up studies suggested the benefits may only be temporary and cyclophosphamide toxicity is a concern (Tzouvelekis et al. 2012).

A further multicentre, double-blind RCT (Scleroderma Lung Study II) in 142 people with systemic sclerosis-associated interstitial lung disease is ongoing, but this will not be completed until 2015.
This is comparing 24 months of mycophenolate mofetil up to a maximum dose of 1500 mg twice daily with 12 months of oral cyclophosphamide up to a maximum dose of 2 mg/kg daily. The primary end point is FVC%, and secondary end points include TLC%, DLCO%, fibrosis score, breathlessness, health-related quality of life, modified Rodnan skin score, and adverse events.

A systematic review and meta-analysis of observational studies of mycophenolate for the treatment of systemic sclerosis-associated interstitial lung disease was published in 2012 (Tzouvelekis et al. 2012). This included 1 prospective observational study of mycophenolate sodium (Simeon-Aznar et al. 2011), 4 retrospective observational studies of mycophenolate mofetil (Koutroupas et al. 2010, Gerbino et al. 2008, Zamora et al. 2008 and Liossis et al. 2006) and 1 unpublished retrospective study of mycophenolate mofetil.

The meta-analysis included a total of 69 people who met American College of Rheumatology criteria for systemic sclerosis, all of whom had evidence of systemic sclerosis-associated interstitial lung disease. Most patients were female (44/69; mean age 53 years) and had mild-to-moderate disease severity as assessed by lung function (FVC% 64% to 79.5%). No information was given on the dose of mycophenolate used.

The main efficacy outcome was lung function (FVC% and DLCO%), which had to be assessed before and at least 6 months after mycophenolate treatment. The meta-analysis used weighted mean differences to summarise differences between these continuous variables before and after treatment. No statistically significant difference was seen for either outcome. For FVC%, the weighted mean difference was 1.48% (95% CI −2.77 to 5.72%, p=0.49), and for DLCO% it was −0.83% (95%CI −4.75 to 3.09%, p=0.93). Individually, the 6 studies found mean differences in FVC% from baseline to the end of treatment of −2.6%, 0%, 4.3%, 4.73%, 7.6% and 10.6%.

A further observational study of mycophenolate for the treatment of systemic sclerosis-associated interstitial lung disease was published in 2013 (Panopoulos et al. 2013). In this single-centre, retrospective case-control study, 10 people with systemic sclerosis who had received mycophenolate mofetil (n=3) or mycophenolate sodium (n=7) for at least 1 year for progressive interstitial lung disease were matched with 10 people who had received oral (n=8) or intravenous (n=2) cyclophosphamide. The duration of mycophenolate treatment ranged between 22 and 72 months, at a mean daily dose of 1500 mg mycophenolate mofetil or equivalent (treatment was started at a daily dose of 2000 mg or more in 8 people. The mean daily dose of cyclophosphamide was 90 mg for between 17 and 55 months. Most patients were female (18/20; mean age 47 years), with a mean FVC% at baseline of 79% in the mycophenolate group and 77.3% in the cyclophosphamide group.
There was no statistically significant change in lung function (as assessed by FVC%, DLCO% and TLC%) from baseline in either group. After 2 years of treatment, the difference from baseline in the mean FVC% was 2.2±11.4% with mycophenolate (p=0.444) and 5.2±12.4% with cyclophosphamide (p=0.326). In each group, lung function remained stable in 6 people, improved (FVC increase of more than 10%) in 3 people and deteriorated (FVC decrease of more than 10%) in 1 person.

Eight people from each group had high-resolution computed tomography scans. After 2 years of treatment, people receiving mycophenolate were found to have more severe progression of interstitial lung disease. There was a statistically significant radiological deterioration of lung function with mycophenolate (from a mean score at baseline of 10.0±8.9 to 12.7±8.2, p=0.039) but not with cyclophosphamide (from 14.5±7.4 to 16.5±5, p=0.197), and the authors suggest that an eagerness to replace cyclophosphamide with mycophenolate is not supported by their findings. However, results of the Scleroderma Lung Study II are awaited to clarify the comparative efficacy and safety of these 2 drugs.

By way of some comparison, in the Scleroderma Lung Study (Tashkin et al. 2006), the mean absolute difference in adjusted 12-month FVC% between the cyclophosphamide and placebo groups was 2.53% (95% CI 0.28% to 4.79%), favouring cyclophosphamide (p<0.03). Defining what a clinically important difference in FVC% is for people with scleroderma is difficult because of the limited evidence base. Differences of 10% have previously been suggested to be clinically significant, but more recently lower differences of 2 to 6% have been estimated as the minimal clinically important difference (Panopoulos et al. 2013). The authors of the Scleroderma Lung Study stated that the clinical importance of the small treatment effect seen on FVC% was supported by the additional findings that cyclophosphamide improved dyspnoea, skin thickening, and functional ability (based on HAQ-DI).

The authors of the meta-analysis (Tzouvelekis et al. 2012) discuss that as lung function deteriorates over time in people with systemic sclerosis-associated interstitial lung disease, a marginal increase in FVC or even stabilisation of lung function with the use of mycophenolate could be clinically important. However, the authors of the case-control study (Panopoulos et al. 2013) suggest that in a proportion of people with systemic sclerosis-associated interstitial lung disease, impairment of lung function is minimal and shows limited progression. Therefore, stability in lung function could be attributed to the actual physical history of the disease and not to any drug treatment.

Mycophenolate has also been studied in a wider population of people with connective tissue disease-associated interstitial lung disease (Fischer et al. 2013). In this retrospective single-centre cohort study, 125 people (44 of whom had systemic sclerosis-associated interstitial lung disease) received mycophenolate mofetil for a median of 897 days (at a dose of 3000 mg daily in most
people. For the entire cohort, mycophenolate mofetil was associated with statistically significant improvements in FVC% (7.3±2.6% at 156 weeks, p=0.004) and in DLCO% (7.1±2.8% at 104 weeks, p=0.01). For the subgroup of people with systemic sclerosis-associated interstitial lung disease, the authors state that FVC% and DLCO% were trending downward before mycophenolate treatment was started and then trended upward after treatment initiation. However, the data presented in the paper are incomplete and difficult to analyse.

Safety and tolerability

In the prospective observational study that estimated the relative effectiveness of 5 different treatment approaches in 147 people with early diffuse cutaneous systemic sclerosis, 3 treatment protocols included mycophenolate mofetil (Herrick et al. 2010). In protocol 1 (intravenous cyclophosphamide followed by mycophenolate mofetil), 16 out of 29 people (55%) reported adverse effects. In protocol 2 (antithymocyte globulin followed by mycophenolate mofetil), 10 out of 25 people (40%) reported adverse effects, and in protocol 3 (mycophenolate mofetil alone), 27 out of 61 (44%) reported adverse effects. No information was given on the nature of these adverse effects.

In the prospective observational study in 25 people with previously untreated recent-onset diffuse cutaneous systemic sclerosis (Mendoza et al. 2012), there were no discontinuations because of adverse effects, but 3 people had their dose of mycophenolate mofetil reduced to between 1000 mg and 1500 mg daily because of gastrointestinal adverse effects. A total of 13 adverse events were recorded in 10 people: diarrhoea (n=3), upper respiratory infections (n=3), lymphopenia (n=2) and urinary tract infection (n=2). One person died 18 months after study entry from severe and rapidly progressive cardiomyopathy, the cause of which could not be conclusively established.

A further retrospective single-centre cohort study (Nihtyanova et al. 2007) assessed the tolerability of mycophenolate mofetil in 109 people with diffuse cutaneous systemic sclerosis. Most people (79%) had received mycophenolate for at least 1 year, most commonly at a dose of 2000 mg daily. Mycophenolate mofetil was discontinued in 34% of people, in 8% because of adverse effects. Adverse reactions were reported in 12% of people, most commonly gastrointestinal tract disturbances (4.6%) and infections (3.7%).

In the systematic review and meta-analysis of observational studies of mycophenolate for the treatment of systemic sclerosis-associated interstitial lung disease (Tzouvelekis et al. 2012), the authors state that mycophenolate mofetil was well tolerated by the vast majority of the 69 people included in the studies. No cases of liver toxicity, clinically significant infection or leucopenia were
recorded during treatment. One person developed nausea that led to drug discontinuation, and another had transient abdominal pain and nausea. One person had *Aspergillus terreus* pulmonary infection that was treated with voriconazole and mycophenolate sodium suppression.

In the retrospective cohort study in the wider population of 125 people with connective tissue disease-associated interstitial lung disease (*Fischer et al. 2013*), mycophenolate mofetil was discontinued in 10% (n=13) of people. Reasons for discontinuation included gastrointestinal intolerance (n=3), interstitial lung disease progression (n=2), hepatic transaminase elevation (n=2), recurrent infections (n=1), cytopenias (n=1) and non-specific symptoms (n=4).

The summaries of product characteristics (SPCs) for mycophenolate mofetil and mycophenolate sodium (*Myfortic*, Novartis) state that people receiving immunosuppressive regimens involving combinations of medicines that include mycophenolate, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. They also state that people receiving immunosuppressants, including mycophenolate, are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections and sepsis. The SPCs advise that people taking mycophenolate should report immediately any evidence of infection, unexpected bruising, bleeding or anything else that indicates bone marrow depression.

The SPCs advise that people taking mycophenolate should be monitored for neutropenia, and have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. They also state that because mycophenolate has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, haemorrhage and perforation, it should be used with caution in people with active serious digestive system disease. People should also be advised that during treatment with mycophenolate, vaccinations may be less effective, and the use of live attenuated vaccines should be avoided.

The SPCs recommend that mycophenolate should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning mycophenolate therapy, during therapy, and for 6 weeks after therapy has stopped.

In July 2009, the Medicines and Healthcare products Regulatory Agency (MHRA) warned about the risk of pure red cell aplasia with mycophenolate mofetil in a *Drug Safety Update*. The MHRA advised that, under specialist supervision, mycophenolate mofetil should be discontinued or the dose reduced in people who develop pure red cell aplasia. This warning is included in both mycophenolate mofetil and mycophenolate sodium (*Myfortic*, Novartis) SPCs.
SPCs for mycophenolate mofetil also state that there have been isolated reports of interstitial lung disease and pulmonary fibrosis in people treated with mycophenolate in combination with other immunosuppressants, some of which have been fatal.

**Evidence strengths and limitations**

Scleroderma is a rare condition and RCTs are difficult to undertake. There are no published RCTs of mycophenolate for treating scleroderma, and this evidence summary is, therefore, based on observational studies. All observational studies have limitations inherent in their non-randomised design, particularly around selection bias. The characteristics of the patients selected for treatment with mycophenolate in these studies may have differed from the wider population of patients with scleroderma from which they were drawn, which may have affected the outcomes. Many of the studies were retrospective and were limited by a lack of prospectively defined, systematic methods for data collection, treatment initiation and dosing, and surveillance for adverse effects.

Because scleroderma is a rare condition, studies of mycophenolate have generally been conducted in small numbers of patients. The numbers of patients included in the studies reviewed in this evidence summary ranged from 20 to 147. The meta-analysis (Tzouvelekis et al. 2012) included 6 observational studies, but just 69 patients. Small numbers of patients limit the statistical power of these studies to be able to detect differences in efficacy outcomes. Small patient numbers also limit the safety data that these studies can provide. Less common adverse effects could have been missed and because these studies were observational, adverse effects may not have been recorded in detail in all patients.

Most studies of mycophenolate have been single-arm, open-label studies, with no control group, which compared outcomes before and after mycophenolate treatment. The symptoms of systemic sclerosis can fluctuate over time, and the absence of a control group in the studies means that any changes in outcomes, such as stability in lung function or improvements in skin scores, could be due to the actual physical history of the disease and not to mycophenolate.

In the largest study in this evidence summary, Herrick et al. (2010) included 147 patients and prospectively compared 5 different treatment groups (3 of which included mycophenolate). Standardised entry and follow-up data were collected at baseline, and then at regular intervals for 3 years, which allowed for some comparison of treatment groups. However, patients were not randomised to treatments and although adjustment was made for baseline differences between the groups, residual confounding was still a possibility. There may have been patient- or disease-related variables that could have influenced both the choice of therapy and outcome. Importantly, patients were also allowed to change protocols during the study, and the reasons for
changing could have been related to efficacy. In particular, many people in the 'no disease-modifying treatment' group changed to active treatment during the study, and so the outcomes in this group cannot be taken as the effect of no treatment.

The observational studies reviewed in this evidence summary mainly reported disease-oriented outcomes such as skin score and lung function (FVC%, TLC% or DLCO%). Defining what a clinically important difference is in these outcomes for people with scleroderma is difficult based on the limited evidence base (see above).

RCTs looking at patient-oriented outcomes such as breathlessness, functional ability and health-related quality of life would be useful, and results from the ongoing Scleroderma Lung Study II comparing mycophenolate mofetil with oral cyclophosphamide are eagerly awaited. The primary end point in this RCT is FVC%, but secondary end points include fibrosis score, breathlessness, health-related quality of life, modified Rodnan skin scores, and adverse events. It is not known if mycophenolate has any effect on preventing scleroderma from progressing or on minimising any disability.

Context and estimated impact for the NHS

Cost effectiveness

No cost-effectiveness studies were identified that assessed the use of off-label mycophenolate for treating scleroderma.

The table below gives costs for some of the immunosuppressants used in scleroderma. None of these drugs is licensed specifically for use in people with scleroderma and use of any of these would be off-label.

Table 1 Costs of off-label immunosuppressants used in scleroderma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose</th>
<th>Estimated annual cost excluding VAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (oral)</td>
<td>15 mg per week</td>
<td>£28.97b</td>
</tr>
<tr>
<td>Cyclophosphamide (intravenous)</td>
<td>15 mg/kg per month</td>
<td>£204.72c</td>
</tr>
<tr>
<td>Cyclophosphamide (oral)</td>
<td>2 mg/kg per day</td>
<td>£774.17d</td>
</tr>
<tr>
<td>Mycophenolate mofetil (oral)</td>
<td>1000 mg twice daily</td>
<td>£345.14b</td>
</tr>
<tr>
<td>Mycophenolate sodium (oral)</td>
<td>720 mg twice daily</td>
<td>£2353.40e</td>
</tr>
</tbody>
</table>
a Doses taken from the summaries of product characteristics for other indications and expert opinion. None of these drugs is licensed specifically for scleroderma and use would be off-label. The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

b Costs taken from the Drug Tariff, June 2014. Costs are given excluding VAT.

c Costs taken from the BNF, June 2014. Costs are given excluding VAT. Based on 70 kg adult given 1×1 g vial monthly.

d Costs taken from the Drug Tariff, June 2014. Costs are given excluding VAT. Based on 70 kg adult given 3×50 mg tablets daily.

e Costs taken from MIMS, June 2014. Costs are given excluding VAT.

Current drug usage

No estimate of the current use of off-label mycophenolate for the treatment of scleroderma in UK clinical practice was identified.

In the year from April 2013 to March 2014, 182,606 prescriptions for mycophenolate mofetil that were prescribed in primary care in England were dispensed at a net cost of just under £10 million. For mycophenolate sodium, the figure was 14,779 prescriptions at a net cost of just under £2 million. It is not known how many of these prescription items were for scleroderma (personal communication: NHS Business Services Authority, May 2014).

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with scleroderma who are thinking about trying mycophenolate.

Relevance to NICE guidance programmes

There is currently no NICE guidance on the treatment of scleroderma.

NICE has issued guidance that includes recommendations for licensed indications of mycophenolate mofetil and mycophenolate sodium:
Immunosuppressive therapy for renal transplantation in adults (NICE technology appraisal guidance 85) states that:

- Mycophenolate mofetil is recommended for adults as an option as part of an immunosuppressive regimen only: where there is proven intolerance to calcineurin inhibitors, particularly nephrotoxicity leading to risk of chronic allograft dysfunction, or in situations where there is a very high risk of nephrotoxicity necessitating minimisation or avoidance of a calcineurin inhibitor.

Immunosuppressive therapy for renal transplantation in children and adolescents (NICE technology appraisal guidance 99) states that:

- Mycophenolate mofetil is recommended as an option as part of an immunosuppressive regimen for child and adolescent renal transplant recipients only when: there is proven intolerance to calcineurin inhibitors, particularly nephrotoxicity which could lead to risk of chronic allograft dysfunction, or there is a very high risk of nephrotoxicity necessitating the minimisation or avoidance of a calcineurin inhibitor until the period of high risk has passed.

- The use of mycophenolate mofetil in corticosteroid reduction or withdrawal strategies for child and adolescent renal transplant recipients is recommended only within the context of randomised clinical trials.

- Mycophenolate sodium is currently not recommended for use as part of an immunosuppressive regimen in child or adolescent renal transplant recipients.

NICE has also issued guidance on idiopathic pulmonary fibrosis (NICE clinical guideline 163). This includes mycophenolate mofetil in a list of drugs which are not recommended for use, either alone or in combination, to modify disease progression in idiopathic pulmonary fibrosis.

References

European Scleroderma Observational Study: treatment outcome in early diffuse cutaneous systemic sclerosis [online; accessed 12 June 2014]


Herrick AL, Lunt M, Whidby N et al. (2010) Observational study of treatment outcome in early


NHS Choices (2014) Scleroderma [online; accessed 16 May 2014]


Novartis Pharmaceuticals UK Ltd (2013) Myfortic gastro-resistant tablets summary of product characteristics [online; accessed 16 May 2014]


Roche Products Limited (2013) Cellcept summaries of product characteristics [online; accessed 16 May 2014]


Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.
About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

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ISBN 978-1-4731-0673-4