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Title:
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Date:
2017-04-01

Citation:
Boulos, D., Ngian, G. S., Rajadurai, A., Elford, K., Stevens, W., Proudman, S., Owen, C., Roddy, J., Nikpour, M., Youssef, P., Hill, C. & Sahhar, J. (2017). Long-term efficacy and tolerability of mycophenolate mofetil therapy in diffuse scleroderma skin disease. International Journal of Rheumatic Diseases, 20 (4), pp.481-488. https://doi.org/10.1111/1756-185X.13035.

Received Date : 02-Aug-2016

Revised Date : 24-Oct-2016

Accepted Date : 18-Nov-2016

Article type : Original Article

Long-Term Efficacy and Tolerability of Mycophenolate Mofetil Therapy in Diffuse Scleroderma Skin Disease.

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Short Title: Mycophenolate for scleroderma skin.

Word Count: 2,902.

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Funding
The Australian Scleroderma Cohort Study is managed by the Australian Scleroderma Interest Group and supported by the St Vincent's Hospital IT Department and Research Endowment Foundation, Scleroderma Australia, Arthritis Australia and unrestricted educational grants from Actelion Australia, GSK and Pfizer.

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Abstract

Objectives: To assess the long-term efficacy and tolerability of mycophenolate mofetil (MMF) in patients with diffuse cutaneous systemic sclerosis (dcSSc).

Methods: Patients enrolled in the Australian Scleroderma Cohort study with dcSSc and baseline modified Rodnan skin score (mRSS)≥12 who were treated for a minimum of 12 months with MMF for the primary indication of skin disease were included and their prospectively collected data retrieved. Change in mRSS, the proportion with a clinically significant improvement (reduction in mRSS≥5 from baseline) and adverse effects due to therapy were determined.

Results: Seventy-four participants treated with MMF were identified and of these, 42 met inclusion criteria. The mean age was 53±12 years, with mean disease duration at MMF commencement of 4.8±4.3 years. Twenty-one participants (50%) commenced MMF within two years of disease onset and the mean duration of therapy was 2.7±1.7 years. The mean mRSS at baseline was 25.9±9.2 with a reduction of 3.7±7.1 (p-value=0.07) after one year of therapy, 7.6±8.3 after two years (p-value=0.01) and 10.5±10.3 after five years (p-value<0.01). Response to treatment was not affected by disease duration at MMF commencement or baseline skin score. Eighteen participants (43%) demonstrated clinically

significant improvement after one year, increasing to 92% after four years. Two participants (5%) ceased MMF due to adverse effects.

Conclusion: MMF was associated with a modest improvement in mRSS and was well tolerated in the treatment of dcSSc. Given the natural history of dcSSc where skin involvement can spontaneously improve, randomized, placebo-controlled studies are required to confirm whether improvement can be attributed to MMF therapy.

Word count: 249
Keywords: Systemic sclerosis, Mycophenolate mofetil, Scleroderma,Diffuse.

Introduction

Systemic sclerosis (SSc) is a heterogeneous, autoimmune disorder of unknown aetiology, characterised by immune dysregulation, microvascular disease and excess collagen deposition (1). It can result in organ dysfunction, reduced physical function and quality of life and premature mortality. Skin involvement in diffuse SSc (dcSSc) can be extensive and result in progressive debility. A variety of immunosuppressive agents have been trialled in SSc (2), including methotrexate, which has shown modest benefit in two randomised controlled trials for skin manifestations in early dcSSc and is recommended for treatment of dcSSc in the 2008 EULAR recommendations (3), as well as cyclophosphamide (CYC), which has recently been shown to lead to improvement in interstitial lung disease (ILD) and skin thickening in randomised control trials of patients with diffuse or limited SSc (4).

Mycophenolate mofetil (MMF), a lymphocyte anti-proliferative agent, exerts its anti-inflammatory effects primarily through the blockade of de novo purine synthesis in B and T lymphocytes (5). It has also been demonstrated in vivo to down regulate production of transforming growth factor beta, which is thought to result in reduced deposition of extracellular matrix and hence is a promising therapy in fibrotic disorders (6). MMF has been associated with improvement in skin thickening in several observational studies in SSc (7-9), and more recently, in the Scleroderma Lung Study II (SLS II) (10). This randomised controlled study compared the effect of CYC and MMF on forced vital capacity (FVC) in ILD in patients with diffuse or limited SSc. SLS II demonstrated modest and similar improvements in FVC and modified Rodnan skin score (mRSS) in both treatment groups at two years with MMF being better tolerated (10). Given its more favourable side-effect profile, MMF may be an effective and safer alternative to CYC.. In this observational study, we

report our practical experience of the use of MMF prescribed primarily for the indication of skin disease. This cohort, derived from the Australian Scleroderma Cohort Study (ASCS) represents one of the largest studies to date of prospectively collected data examining the efficacy and tolerability of MMF therapy in the management of skin disease in dcSSc. Moreover, long-term toxicity and maintenance of effect is assessed in a subgroup of patients treated for up to five years with MMF.

Methods

Subjects

Patients were recruited from the ASCS, - a prospective, multicentre, longitudinal study of disease outcomes in patients with SSc. These participants are over 18 years of age, fulfil the American College of Rheumatology or Leroy and Medsger criteria for SSc (11, 12) and give written, informed consent. Patients with dcSSc seen between January 2007 and November 2015 who were treated with MMF for a minimum of 12 months for the indication of skin involvement were identified. Diffuse disease was defined as skin thickening of the proximal limb or trunk and for the purpose of this study, only those patients with a mRSS≥12 were included in line with recent studies (7). Skin scores were measured and recorded annually and those with a mRSS<12 at baseline, primary indication for MMF other than skin, or less than 12 months of therapy were excluded from efficacy analysis. Disease duration was measured from the onset of the first non-Raynaud's symptom. The ASCS was approved by the relevant human research ethics committees at each of the participating centres (Royal Perth Hospital Ethics Committee, Royal Adelaide Hospital Research Ethics Committee, St Vincent's Human Research Ethics Committee A, Monash Health Human Research Ethics Committee, Tasmanian Health and Medical Human Research Ethics Committee and University of Wollongong Human Research Ethics Committee).

Data Collection

Baseline demographics, disease subtype and duration, serology, organ involvement, serial pulmonary function tests, oral aperture, presence of tendon friction rubs, treatment data and mRSS were retrieved from the database. ILD was defined as the presence of interstitial abnormalities on high-resolution CT or lung biopsy and renal crisis as the presence of at least two of the following: new onset hypertension, microangiopathic anaemia or rising creatinine. Treating physicians from each centre were contacted to confirm previous and current therapy for skin disease, the dose and indication for MMF therapy as well as adverse effects and reasons for cessation.

The changes in serial mRSS from the date of MMF commencement were analysed with associated clinical data, censored on 30th November 2015. The primary outcome was reduction in mRSS. We defined clinically significant improvement in skin thickening as a reduction in mRSS≥5 from baseline as per the EUSTAR analysis of predictors of improvement in skin fibrosis (13). Stable disease was defined as a change in mRSS<5, whilst clinical deterioration was defined as an increase in mRSS≥5. Further analysis of a subgroup of patients with disease duration less than two years at time of MMF commencement was performed to assess the impact of shorter disease duration on change in skin scores over time. Change in FVC was analysed as a measure of response for ILD.

Statistical Methods

The mean ± standard deviation was used to describe continuous variables and percentage was used to describe categorical variables. The paired t-test was used to compare mRSS pre and post MMF therapy. P-values ≤0.05 were considered significant. All statistical analyses were performed using Graphpad Prism®.

Results

Study Population

Three-hundred and eighty-one patients from the ASCS were identified as having diffuse SSc. Of these, 68 were identified as ever having been treated with MMF. Eighteen of these were on MMF for less than 12 months and eight were on MMF for a primary indication other than skin, leaving 42 patients for inclusion in the efficacy analysis (Table 1). The mean age of participants was 53±12 years with 35 (83%) being female. Thirty-four (81%) participants were Caucasian, whilst seven (17%) were of Asian descent. The mean duration of disease prior to MMF commencement was 4.8±4.3 years, with 21 (50%) participants commencing MMF within two years of disease onset.

The vast majority (98%) of the cohort were ANA positive, with speckled (48%) and homogeneous (43%) patterns being the most prevalent. Seventeen (40%) were anti-topoisomerase antibody positive and 11 (26%) were RNA polymerase III antibody positive. Sixteen (38%) participants had ILD, defined as fibrosis on chest high-resolution computed tomography, whilst three (7%) had a history of renal crisis. The mean mRSS for the entire cohort at baseline prior to MMF commencement was 25.9±9.2. This was not significantly different from those commenced on MMF within two years of disease onset, with a baseline mRSS of 27.2±9.6 (p-value= 0.61). Six patients (14%) had a baseline mRSS≤22.

<Insert Table 1 here>

Compared to a cohort of 339 patients identified from the ASCS who presented with diffuse disease over the study period and who were not commenced on MMF for skin ("baseline cohort"), the MMF cohort had a shorter disease duration (4.8±4.4 vs 8.8±8.6 years; p<0.01), a higher mRSS (25.9±9.2 vs 20.3±9.9; p<0.01) and lower FVC (82.6±20.4 vs 89.5±20.2%; p=0.04). There was no significant difference between rates of ILD and prevalence of renal crisis.

Therapy

The mean duration of therapy was 2.7±1.7 years with a mean dose of 1.9±0.4 grams per day. Twenty-seven (61%) participants had been previously treated with prednisolone, whilst 19 (45%) were on prednisolone concurrently with MMF therapy. Nineteen (45%) participants had been treated with a disease-modifying agent other than MMF prior to study commencement (Table 2) with two of these patients ceasing previous therapy due to adverse events and 11 due to inefficacy. Of the patients who had previously been treated with CYC, one received intravenous therapy and eight received oral CYC. The mean period in between receiving methotrexate, AZA, CYC and MMF was 2.3±2.2, 1.5±0.5, 2.7±2.4 years respectively, with two patients (5%) receiving CYC within twelve months of MMF.

<Insert Table 2 here>

Outcome variables

At the censor date, all participants had completed at least twelve months of MMF therapy (n=42), 28 had been on therapy for at least two years (67%), 12 had completed four (29%) and ten had completed five years of therapy (24%) (Table 3). There was a mean reduction in mRSS of 3.7±7.1 in the first year of therapy, 3.4±6.1 in the second, 1.9±4.6 in the third and 0.9±6.3 after the fourth . There was a total reduction in mean mRSS of 10.5±10.3 after five years of therapy (Figure 1). The improvement in mean mRSS after the second year of therapy as well as each subsequent year was statistically significant.

<Insert Figure 1 here>

<Insert Table 3 here>

Participants who were commenced on MMF within two years of disease onset demonstrated similar reduction in skin scores to the entire cohort, with 1.9±7.1 after the first year of

therapy, a further 4.8±5.3 reduction after the second, and a total reduction of 11.4±11.3 by five years.

Eighteen (43%) participants achieved clinically significant improvements in skin score after one year of MMF therapy. Of those who had been treated for two years and four years or more, this was increased to 61% and 92% respectively (Figure 2). There was no significant difference in baseline mRSS between clinically significant responders and non-responders (p-value 0.19). In those commenced on MMF within two years of disease onset, 29% and 39% demonstrated clinically significant improvement after one and two years respectively, whereas 100% of this subset achieved clinically significant improvement within four years of MMF therapy.

<Insert Figure 2 here>

There was no significant change in pulmonary function, with mean FVC at study commencement of 82.6±20.4% predicted, compared to a mean FVC of 82.0±20.2% at end of study (p-value 0.74). There was also no significant difference between oral aperture measurement (4.0±0.8 vs 4.0±0.9cm; p-value 0.92) and the presence of tendon friction rubs (5 vs 1 patients; p-value 0.20) pre and post MMF therapy.

Of the 19 patients on concurrent prednisolone, the median daily prednisolone dose on MMF initiation was 5.0mg [interquartile range: (IQR) 0-10.0] with a significant reduction in median daily dose at censor date to 1.0mg (IQR 0-8.7; p-value<0.05).

Tolerability

Of the 42 patients treated with MMF, two (5%) ceased therapy due to drug inefficacy after twelve months. Four patients (10%) experienced adverse effects, although this warranted cessation of therapy in two (5%), one with severe diarrhoea within two years of commencing therapy, and one with recurrent infections after five years. Of the initial 74 patients with dcSSc who started MMF, seven patients ceased MMF before 12 months; four due to disease improvement and three because of inefficacy. No patients who ceased MMF prior to 12 months did so due to adverse effects.

Discussion

Diffuse cutaneous SSc is characterised by extensive and often debilitating skin fibrosis and thickening. While many disease modifying agents have been trialled to ameliorate these

changes, until recently, none have demonstrated substantial improvement in diffuse skin disease with acceptable drug tolerability (14). Studies of the natural history of diffuse skin disease in SSc demonstrate a progressive increase in mRSS up to 18 months prior to a gradual, spontaneous improvement over time in many patients (15). The likelihood of progression remains difficult to predict although, short disease duration, synovitis and low baseline skin score (mRSS≤22) have been identified as predictors of an increasing skin score (16). The heterogeneous nature of the disease as well as the tendency toward spontaneous improvement and reluctance of clinicians to treat with placebo has made it difficult to conduct randomised controlled trials of novel therapies (17).

In this prospective, observational study of 42 patients with diffuse skin disease taking MMF for the primary indication of skin thickening, MMF was associated with modest improvements in skin scores with a fall in mean mRSS of 3.7 at 12 months and 7.6 at 24 months. This concurs with the findings of Mendoza *et al* (7), who demonstrated a mean fall in mRSS of 10.9 after 18 months of MMF therapy in 25 patients with early disease (<2 years), with a reduction in accumulation of fibrotic tissue as well as real time PCR demonstrating reduced expression of fibrosis related genes in skin biopsies. In a larger, retrospective study by Le *et al* (9) of 98 patients with a median disease duration of 12.5 months and a baseline mRSS of 23 and a smaller prospective study by Derk *et al* (8) of 15 patients with a mean disease duration of 13.4 months and baseline mRSS of 22, skin score reductions of 7.9 and 14 respectively were seen at 12 months. However, larger doses of MMF up to 3g were utilised in these studies with potential for greater benefit.

To account for variable patient characteristics and response to therapy, we also determined the number of patients who achieved a significant improvement in mRSS (≥5) and found that 43%, 61% and 92% demonstrated improvement in mRSS at 12, 24 and 48 months respectively. We noted a similar reduction in skin score in those with disease duration less than two years, although, onset of improvement was delayed. This may be explained by the fact that those with shorter disease duration who warrant therapy are more likely to have rapidly progressive disease and are more likely to worsen before any improvement as a result of therapy becomes readily apparent (16). This is supported by our findings that those with dcSSc who were commenced on MMF for skin disease had a shorter disease duration than those who were not (4.8±4.4 vs 8.8±8.6 years; $p<0.01$). Whilst an mRSS≤22 has been suggested as predictor of disease progression (16), this was not able to be meaningfully assessed given the low proportion of patients with a mRSS≤22 at baseline, however, we did not find a greater improvement in skin scores in those with a higher baseline mRSS.

In the recent SLS II study in which skin scores were examined as a secondary outcome in patients with SSc and ILD, patients with a mean disease duration of 2.5 years were treated for ILD with two years of MMF (3g per day) or one year of CYC followed by one year of placebo therapy. Compared to preliminary data from the SLS II study, our findings demonstrate a greater reduction in mRSS from baseline at 24 months (7.6±8.1 vs 4.9 ± 1.0). However, it is worth noting that the SLS II trial included patients with diffuse (56%) and limited SSc (44%), with a lower mean baseline mRSS (15.3±10.4 vs 25.9±9.2 in our study). Interestingly, this group found a similar percentage of patients with a significant improvement in skin score at two years (68% vs 61%).

Given the lack of a placebo group in our study, we compared the changes in mRSS observed in our study to historical controls from previous randomised control trials. Baseline mRSS was not dissimilar to that of a trial of oral bovine type 1 collagen (collagen) (25.9±9.2 vs 26.1±7.8) (18), however, was significantly higher than that in the trial of D-penicillamine (D-pen) and the diffuse SSc patients in the SLS I trial of CYC (25.9±9.2 vs 21.0±8.0 and 20.2±9.3 respectively) (19, 20). Whilst we found a reduction of mRSS of 3.7±7.1 at 12 months, these studies reported reductions of 3.4±7.1, 2.5±8.6 and 1.7±6.9 respectively. The D-pen study also reported reduction in mRSS of 4.9±2.7 at 24 months (17), which is similar to the reduction of 7.8±8.1 we found in our study. Given that duration of these studies was limited to 24 months, we cannot determine whether the ongoing improvement identified in our study up to five years of therapy would surpass the degree of improvement in controls from previous studies. However, our study highlights that longer term studies (up to five years) are required to determine the benefits of treatment for skin disease in dcSSc.

Our experience with MMF was not dissimilar to that of Pope *et al* (21) and their randomised control trial comparing methotrexate to placebo in dcSSc. Their reported reduction in mRSS of 4.1±3.4 after one year of therapy was not significantly different to our results of 3.7±7.1. However, our improvement in skin scores are significantly greater than that of the experience of Van den Hoogen *et al* (22), who reported a reduction in mRSS of 1.12±6.5 in their cohort of 17 patients after twelve months.

While MMF was commenced primarily for skin thickening, pulmonary function remained stable on therapy. This is in contrast to other studies of MMF in the treatment of SSc-ILD which showed modest improvements in FVC (7, 8, 23-25); however, this can be explained by the high baseline FVC in our cohort and the low rates of concurrent, progressive ILD. Oral aperture also remained unchanged over the period of follow-up. While there was a trend to improvement in tendon friction rubs, given the low baseline incidence, this did not reach

statistical significance. As has been demonstrated by Fischer *et al* in SSc-ILD (26), we observed a reduction in concurrent use of prednisolone whilst on MMF therapy.

MMF was well tolerated, with only 5% ceasing the drug because of adverse events. This is consistent with other studies which have demonstrated superior tolerability of MMF compared to CYC (10) and azathioprine (25). Where the high cost of MMF has previously been a barrier to its use in SSc skin disease, the recent introduction of generics may allow easier access to its use in the future.

The strengths of our study include its prospective nature, standardised data collection and the inclusion of patients with only diffuse disease. Although our sample size of 42 is modest, it compares favourably with the number of patients with diffuse disease examined in the SLS II study (n=38) and Mendoza study (n=25) and is enriched with 50% of patients with early disease which is more likely to be associated with skin progression. Whereas previous studies have been limited to two years of therapy, our study also examines the effect of MMF in a subset of patients up to five years with ongoing improvement in skin scores. Whether improvements seen here can be attributable to MMF or reflects the natural regression of the disease remains unclear.

Limitations of our study include its observational nature and the absence of a control group, such that the modest improvement in skin scores in patients treated with MMF in this study may represent the natural improvement in skin disease over time. The mean dose of MMF therapy in our study (1.9g per day) is also lower than what has been utilised in other SSc trials (10) and higher doses may be associated with a greater response. A larger randomised control trial of high dose MMF for diffuse skin disease will help further elucidate the role of MMF and dosing in dcSSc skin disease.

Conclusions

In this study, MMF was associated with a modest improvement in skin scores regardless of disease duration and was well tolerated in the treatment of dcSSc. Given the natural history of dcSSc where skin involvement can spontaneously improve, placebo-controlled studies are required to clarify the role of MMF therapy in dcSSc skin disease.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Table 1: Baseline charecteristics at MMF commencement.

	Those not treated with MMF for skin	Those on MMF for skin (n=42)	Evidence of difference (p-value*)
Age (years)	54±13	53 ± 12	0.64
Gender (Female/Male)	257/82	35/7	0.34
Ethnicity Caucasian/Asian/Other	289/20/30	34/7/1	0.49
Disease duration (years)	8.8±8.6	4.8 ± 4.4	**<0.01**
mRSS[†]	20.3±9.9	25.9 ± 9.2	**<0.01**
FVC[‡] **(% predicted)**	89.5±20.2	82.6 ±	**0.04**
Current Smoker	48 (14)	4 (10)	0.63
ANA positive	313 (92)	41 (98)	0.34
Anti-topoisomerase	89 (26)	17 (40)	0.07
U1RNP	15 (4)	2 (5)	1.00
RNA Polymerase III	128 (38)	11 (26)	0.17
Interstitial lung disease	141 (42)	16 (38)	0.74
Renal crisis	28 (8)	3 (7)	1.00

Data as mean ± SD for continuous variables and (%) for categorical variables.

[†]modified Rodnan Skin Score [‡]Forced Vital Capacity

Figure 1: Modified Rodnan skin score (mRSS) over duration of MMF therapy

p-value* reflects mean mRSS from baseline.

Table 2: Disease modifying agents used and reason for cessation

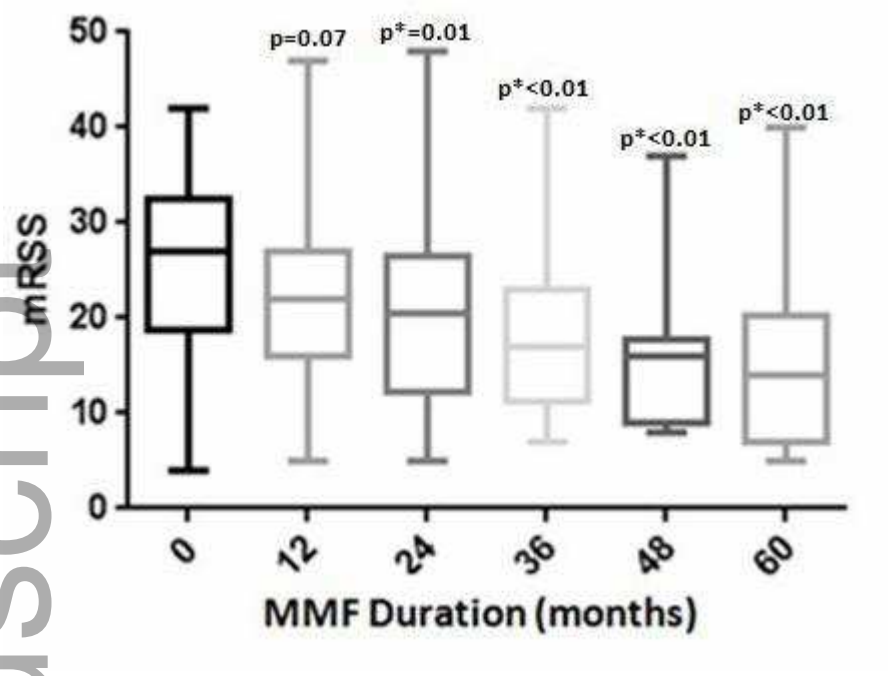
Reason for cessation	**Cyclophosphamide** (n=9)	**Methotrexate** (n=10)	**Azathioprine** (n=2)
Ceased after improvement in non-skin indication	6	1	1

Lack of efficacy	2	8	1
Side effects	1	1	0

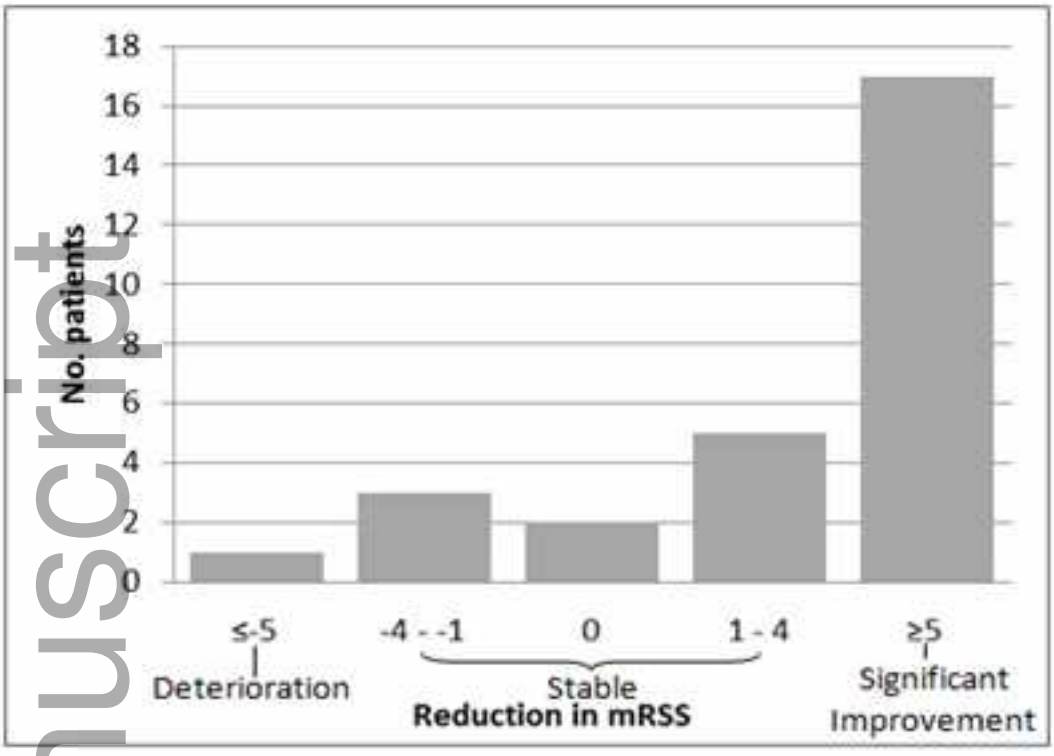
Table 3: mRSS over duration of MMF therapy

Duration of MMF therapy (months)	Baseline	12	24	36	48	60
n=	42	42	28	16	12	10
Mean mRSS	25.9±9.2	22.2±9.1	20±9.2	18.4±8.9	15.7±7.7	15.8±9.7
Annual reduction	-	3.7±7.1	3.4±6.1	1.9±4.6	4.5±4.3	0.9±6.3
Cumulative reduction		3.7±7.1	7.6±8.1	8.1±8.4	9.7±7.0	10.5±10.3
Difference from baseline (p-value)	-	0.07	0.01	<0.01	<0.01	<0.01

Figure 2: Reduction in mRSS after 24months MMF therapy



apl_13035_f1.jpg



apl_13035_f2.png