**Mycophenolate for persistent Complex Regional Pain Syndrome, a parallel, open, randomised, proof of concept trial**

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**Abstract**

Background and aims: Current therapies for persistent Complex Regional Pain Syndrome (CRPS) are grossly inadequate. With accruing evidence to support an underlying immunological process and anecdotal evidence suggesting potential efficacy of mycophenolate, we wished to explore the feasibility and effectiveness of this treatment in patients with CRPS.

Methods: A randomized, open, parallel, proof of concept trial was conducted. Patients with Budapest research criteria CRPS of >2-year duration and moderate or high pain intensity (numeric rating scale score ≥ 5) were enrolled. Eligible patients were randomized 1:1 to openly receive mycophenolate as add-on treatment, or their usual treatment alone, over 5.5 months. They then switched to the other treatment arm for 5.5 months. The main outcome was average the patients’ average pain intensity recorded over 14 days, between 5.0-5.5 months post randomisation, on 11-point (0-10) numeric rating scales, compared between trial arms. Skin sensitivities and additional outcomes were also assessed.

Results: 12 patients were enrolled. Nine provided outcomes and were analysed for the main outcome. Mycophenolate treatment was significantly more effective than control (drug-group mean(SD): pre: 7.4(1.2)-post: 5.2(1.3), n=4, control: pre: 7.7(1.4)- post: 8.1(0.9), n=5; -2.8 (95% CI: -4.7, -1.0), p=0.01, ANCOVA).

There were 4 treatment responders (to mycophenolate treatment either before, or after switch), whose initial exquisite skin hyper-sensitivities, function and quality of life strongly improved. Side effects including itchiness, skin-cryptitis, increased pain, and increased depression caused 45% of the subjects to stop taking mycophenolate.

Conclusions: Mycophenolate appears to reduce pain intensity and improve quality of life in a subgroup of patients with persistent CRPS

Implications: These results support the feasibility of conducting a definite trial to confirm the efficacy and effect size of mycophenolate treatment for persistent CRPS (EudraCT 2015-000263-14).

**Keywords:** CRPS, complex regional pain syndrome, mycophenolate, pain, DMARD

**Introduction:**

Complex Regional Pain Syndrome (CRPS) is a severe chronic painful condition, which typically affects distal limbs following injury. Whereas most patients improve within the first 1-2 years after onset 15% develop persistent CRPS, characterized by unrelenting pain and associated with amongst the lowest quality of life scores in any medical condition [[1](#_ENREF_1), [2](#_ENREF_2)]. Invasive neuromodulation can reduce CRPS-pain in about 50% of patients [[3](#_ENREF_3)], but no practical drug treatment has yet been established and many patients cannot be treated at all. Most patients with CRPS have specific anti-autonomic immunoglobulin G serum- autoantibodies, which are not present in other chronic pain conditions, and the transfer of serum-immunoglobulin G from patients to rodents elicits CRPS-like signs in the animals following hind paw injury[[4](#_ENREF_4), [5](#_ENREF_5)]. These features suggest that autoantibodies contribute to the pathophysiological process underlying persistent CRPS. Treatment of 5 CRPS patients with mycophenolate, an immunosuppressant with known efficacy in autoantibody-mediated rheumatological and neurological conditions, has been reported anecdotally[[6](#_ENREF_6)], but to our knowledge no controlled trial of this treatment has been performed. We conducted an open, randomized controlled trial, to gain proof of concept data on mycophenolate-activity, and the feasibility of this treatment in persistent CRPS.

**Patients and Methods:**

*Study Design and Participants*

The ‘*mycophenolate for the treatment of persistent complex regional pain syndrome*’ (MYPS 1) trial was a single centre, randomized, open, parallel, add-on trial with obligatory switch to the other treatment after completion of the parallel phase, in participants with persistent Complex Regional Pain Syndrome (EudraCT 2015-000263-14). The recruitment centre was a tertiary Pain Management Unit in Northern England. Ethics approval was given (15/NW/0135 North-West Ethics, Manchester). The study protocol is provided in the web-appendix.

Eligible participants were non-pregnant adults with moderate or severe CRPS of at least 2 years’ duration, fulfilling Budapest research criteria[[7](#_ENREF_7)] and with no other important pains. A mean pain intensity of 5 or higher on an 11-point (0-10) Numeric Rating Scale (NRS) was required for entry into the trial. Before enrolment, patients had tried tricyclic antidepressants, gabapentinoids, mild and strong opioids, and completed a course of specialized pain physiotherapy, unless contraindicated, or refused. Mycophenolate-specific exclusion criteria applied (trial protocol page 4, web-appendix: history of any past or current cancer, specific contraindication to mycophenolate, at screening renal failure or serum creatinine >1.5 x upper limit normal or any single liver enzyme value raised >150% upper limit normal, any blood dyscrasia with cell count <80% lower limit normal, any acute or recent infection). Patients with medical conditions which would make trial participation unsafe in the view of the investigator were also excluded. Patients continued any established analgesic medications and rehabilitative exercises throughout the trial.

Participants were recruited from the study centre’s internal database, and from new patients referred to the Principal Investigator (AG). They were provided with patient information leaflets about the trial; interested patients gave written informed consent.

After consent and screening for eligibility, patients completed a screening diary for 14 days reporting their average 24h pain scores, pain unpleasantness scores, and sleep quality (11-point, 0-10 numeric rating scales). These entries were also the baseline-values for the later statistical analysis, see below. Patients whose average screening diary NRS pain score was 5 or higher (details see protocol in the web-appendix) were randomized during a second visit scheduled 3 weeks after screening.

*Study Design*

This was a parallel trial; after 5.5 months all patients were asked to switch to the other treatment, to provide additional data for secondary outcomes.

*Randomisation*

Participants were individually randomly assigned (1:1) to either i) mycophenolate plus usual practice first (‘active’), or ii) usual practice only first (‘control’), by site staff via an independent online randomisation system, based at the King’s Clinical Trials Unit (KCTU), which was not otherwise involved in this trial. The randomisation sequence was concealed.

*Procedures*

The up-titration procedure and safety blood tests followed the British Society for Rheumatology Reference Guide (www.rheumatology.org.uk), and are detailed in the study protocol; the patient flow is indicated in the study Flow-Chart (Figure W1).

Participants completed weekly paper diaries throughout the whole study, and daily paper diaries over 14 days at the end of each trial period. Patients were assessed with mechanical quantitative sensory testing (QST) both at baseline, and at the end of their active treatment, by an independent Neurophysiologist (PS, protocol in the web-appendix). They completed questionnaires at screening, and at the end of each treatment period; details are provided in the study protocol.

*Outcomes*

The main outcome measure was the average 24h NRS pain intensity over a 14-day period starting 5 months after randomization (day 150) versus screening-baseline compared between the ‘active’ and ‘control’ groups. The two additional efficacy outcomes were i) a within group comparison of the average pain relief over the final 14 days of active treatment (received either before, or after switch) in all patients, compared with their pain intensity before active treatment at either screening (for the ‘active’ group), or the end of the control period, and ii) the average change in QST parameters at the end of active treatment, compared with screening-baseline.

The feasibility outcomes were the tolerability of mycophenolate, specified as i) the proportion of patients who cannot tolerate the minimum dose of 500mg BD, and ii) the proportion of patients who tolerate up titration to best effect as per protocol.

Exploratory outcomes included time to pain-return to baseline (-1NRS point) after active treatment, pain unpleasantness and sleep quality (11-point NRS scores concomitantly entered with the pain diary scores), worst pain, treatment effects on function (Brief Pain Inventory Interference Scale[[8](#_ENREF_8)]), quality of life (EQ-5D), mood (Hospital Anxiety and Depression Scale[[9](#_ENREF_9)]), and patient-developed outcomes (on 11-point numeric rating scales) – all completed at both baseline and at the end of each treatment period. The patient-developed questionnaires included ‘use of limb’: ‘how much use do you have of your limb overall’ (0=full use); ‘lack of energy’: ‘has lack of energy affected you/interfered with your activities over the last week’; ‘pain at rest’: ‘what was the average pain intensity on rest over the last week’; ‘affected limb muscle spasms’: ‘if you had muscle spasms in the affected limb, how much have they affected the limb’s function’ (for patients with no muscle spasms 0 was entered); ‘worthwhileness’: ‘how worthwhile is this treatment for you’ (not at all – completely); ‘acceptability’: ‘taking into account your experience of the drug, positive (any pain relief) and negative (any unpleasant side effects), how acceptable is it to you to continue taking it for 5 years?’ Additionally concomitant medications and safety outcomes were recorded; details are provided in the protocol. The study end was 5.5 months after the last control-group participant’s final study visit.

We defined an average difference of two NRS points, between baseline pain intensity and pain intensity at the end of active treatment as an important clinical effect of the drug on an individual level (‘response’, trial protocol web appendix, page 19); differences were rounded to the next full number.

*Statistical analysis*

No formal power-based sample size calculation was performed for this early phase proof of concept study for the main outcome, a comparison of pain scores between groups at the end of the first treatment phase. We planned to obtain outcomes from 5 patients in each of the two trial arms, a total of 10 patients; the anticipated withdrawal rate was 1/6, therefore a total of 12 patients was recruited. The feasibility of the proposed sample size of n=10 to detect a meaningful within-patient analgesic effect (secondary outcome) was evaluated based on detecting a reduction of pain scores after active treatment for all patients combined (i.e. either before, or after switch, see trial protocol in the web appendix). We estimated from a previous trial that the reduction in pain scores would have a standard deviation of 2 NRS units [[10](#_ENREF_10)]. A group reduction in pain scores of 2 NRS units or higher was regarded as important. We calculated that a total sample of 10 patients would have >80% power of detecting such a difference as statistically significant at 5% significance level.

Due to the small sample size, it was thought unlikely that the study would detect a significant group difference for the main outcome. However, an exploratory analysis was performed using analysis of covariance (ANCOVA). The scores at the end of the first treatment period were treated as the outcome variable, with the screening-baseline scores treated as a covariate. The primary analysis included all eligible patients who were randomized, but excluded patients not providing any outcome data. Additionally, a sensitivity analysis used a Last Observation Carried Forward approach to impute missing data values at the end of the treatment period.

‘For the additional efficacy outcome, we compared, using paired t-test, pain scores recorded at the end of active treatment (the combined scores from patients who had active treatment during the parallel treatment phase, and patients who had active treatment after switch), with these patients’ pain scores before active treatment. Descriptive statistics were used to summarize both the feasibility outcomes and exploratory outcomes.

All statistical analyses were conducted using Stata (version 13.1). This trial is registered with clinicaltrialsregister.eu/ctr-search/trial/2015-000263-14/GB

**Results**

Between 12th May 2015 and 21th April 2016, 16 patients were screened for eligibility. Of these, 12 were randomized to active or control arms, and their baseline characteristics are shown in Table 1. Balance was achieved.

Three patients were lost to follow-up during the first treatment period (Figure 1). Therefore, data for the primary analysis was available from 9/12 patients, with 4 in active, and five in control.

Following switch, one additional patient was lost to follow up (not shown). Therefore, data for the additional efficacy outcome, pain relief at the end of active treatment, were available from 8/12 patients.

*Main outcome*

All analyzed patients provided at least 11 pain intensity scores for the primary outcome between days 150-164 (Table W1). The mean difference between the two groups at the end of treatment was -2.8NRS points (n=9, 95% CI -4.7 - -1.0, p=0.01, ANCOVA). Individual patient responses are provided in Table W2. The results from a sensitivity analysis in all 12 patients were also significantly in favor of the active group (mean difference between the two groups -1.9NRS points (n=12, 95% CI -3.7 - -0.1, p=0.04, Table W3).

*Additional efficacy outcomes*

We compared *all* patients’ average 24h pain intensities over the last two weeks of their mycophenolate treatment, with their baseline pain intensities. In the eight patients, for whom full datasets were available, a significant difference was found (-2NRS pain reduction, 95% CI: -3.7, -0.3, p=0.03); a sensitivity analysis including 12 participants also showed significant pain reduction (-1.3NRS, 95% CI: -2.5, -0.1, p=0.04). After mycophenolate treatment, there were 4 treatment –‘responders’ (see method section): 2 patients had >50%, pain relief (at doses of 1.5g BD, and 1.0g BD respectively), one patient had >40% pain relief, and one patient had >25% (but <30%) pain relief (both at doses of 1.5g BD), Table 2. No patient on usual-practice treatment had >10% pain relief (not shown).

QST baseline results were available from all but one patient, who did not wish to get tested. There was evidence in all patients for increased skin-sensitivities in their affected- when compared to a control limb (not shown). Because mechanical QST can be painful, patients with no clinical benefit from the drug were given a choice to opt out of re-testing, and only one of these patients opted to have re-testing. Patients who were classed as mycophenolate-responders demonstrated broad, profound normalization of their skin sensitivities (Table 2 (brush tests), and Table W4), and there was only minimal change in the remaining tested patient (not shown).

*Feasibility outcomes*

*Tolerability:* Five of the eleven patients receiving the drug (45%) were unable to complete treatment over the full 5.5 months treatment period with a minimum dose of 500mg BD due to pain increase (n=2), increased depression, worsening of a pre-existing skin cryptitis, or severe skin itchiness (n=1 each). Four of these five patients had experienced no pain relief at the time of their discontinuation. The remaining patient (#8, Table W2) had reported substantial pain relief on 1g BD and had disposed of her two crutches, to walk unaided, however this reverted to baseline after 6 weeks off drug (not shown).

The proportion of patients who tolerated full up-titration per protocol was 45% (5/11); one additional patient (#1, Table W2) reported moderate pain relief, but dose-limiting nausea on 1g BD, and then tolerated treatment with 500mg BD, with limited benefit.

*Exploratory outcomes*

*Responder analysis:* These ‘responders’ (patients with an average difference of at least two NRS points between baseline pain intensity and pain intensity after active treatment, n=4) experienced a reduction of their pain in all McGill pain sub-qualities, with strong effects on gnawing, hot-burning, tiring-exhausting, piercing, and light-touch pains, contrasted by only little improvements of throbbing and aching pains (supplementary Table W5). A summary of relevant outcomes is provided in Table 2. These four responders had relatively low medication consumption at baseline, with few changes during the trial (supplementary Table W6). Following the end of active treatment, the average weekly pain intensity in the four responders had started to rise by week 10, and had returned to baseline -1NRS points, or higher, by the end of the study (not shown).

*Adverse Events:* The 11 patients reported 130 adverse events on drug. GI-related effects were common. Four adverse events were classed as severe (nausea, blackout followed by fall with facial contusion, skin itchiness). Two events after physical accidents occurring in the same patient were classed as serious and judged as not drug-related. There were no suspected unexpected serious adverse reactions (SUSAR). All adverse events classed as having a potential relation to the study drug had resolved by the end of the study.

*Health Economics:* The QoL gain secured by the responders - converted into Quality Adjusted Life Years (QALYs) – results in 1.77 QALYs over a 10-year period. Assuming, that the estimated costs were £400 per year for drug costs and patient management, the resultant cost per QALY would be £1,875; if the annual costs were £800, the cost per QALY would be £4,011.

*Clinical treatment of MYPS-responders, and two patients with suspected idiosyncratic reactions to mycophenolate*

After their trial participation had ended, clinical DMARD treatment through the UK public healthcare provider (NHS) was provided to seven trial participants, following individual consent. Pt. #1 was up-titrated slowly but developed dose-limiting nausea at 500mg-1g, with only minimal pain relief. She was swapped to Azathioprine, a DMARD with a similar mechanism of action as mycophenolate, but experienced nausea without beneficial effects and was discontinued. Participant #5 wished to become pregnant and was commenced on Azathioprine, which has a more benign risk profile during pregnancy. She reported substantial pain relief on the maximal dose of 200mg OD. The three remaining per-protocol responders (#2, #3, #11) reported pain relief comparable to that in the trial. Following an episode of 2 months with good pain relief, patient #3 then perceived lessened pain relief, but wished to continue. In contrast, beneficial effects had remained stable in patients #2 and #11 for periods of 9 and 4 months respectively (December 2017). Patients #8 who had stopped the drug during the trial following development of skin-cryptitis was re-commenced on mycophenolate under antibiotic cover at the time of manuscript submission. #12, who had experienced skin-itchiness during the trial, was tried on Azathioprim but reported no beneficial effects.

**Discussion**

In this randomized, open proof of concept trial, mycophenolate treatment as an add on to usual practice appeared effective in some patients with persistent complex regional pain syndrome. Overall 4 patients had meaningful pain relief with few adverse reactions, and near-complete normalization of their, initially exquisite, skin sensitivities to brush-stroke. Two additional patients experienced substantial pain relief, but were unable to tolerate long term treatment. Patients receiving usual practice had no reduction of their pain over 5.5 months, consistent with the results of a recent meta-analysis demonstrating that placebo group pain relief in trials in persistent CRPS is minimal [[11](#_ENREF_11)]. Currently, no evidence-based, practical, effective drug treatment for persistent CRPS is available[[12](#_ENREF_12)]. The results of this trial provide preliminary evidence that immune suppression with mycophenolate may be analgesic in a proportion of patients; the conduct of a larger trial appears feasible.

Responders to mycophenolate in this trial reported robust improvements in a wide range of outcomes. Activity participation, quality of life, function, sleep, limb spasm and energy were strongly improved. There were few cognitive side effects, and the four responders rated the ‘worthwhileness’ of having the drug maximal (Table 2).

The mechanism by which mycophenolate reduces chronic pain from CRPS is unknown. CRPS is not associated with joint inflammation, and systemic inflammatory markers are normal. Recent experimental results have underpinned the idea that non-inflammatory autoantibodies contribute to the pathophysiology of both CRPS [[4](#_ENREF_4), [5](#_ENREF_5)], and ‘idiopathic’ chronic pains in rheumatoid arthritis [[13](#_ENREF_13)]; the reported efficacy of plasma exchange treatment in CRPS is consistent with this idea [[14](#_ENREF_14)]. Mycophenolate might act to suppress the production of pathogenic IgG auto-antibodies, however other mechanisms, including a modification of CNS glia cell activation[[15](#_ENREF_15)] might also contribute; more research will be needed to clarify these effects.

We chose this drug over other immune suppressive drugs, as i) anecdotal evidence for activity already existed [[6](#_ENREF_6)], ii) within the disease-modifying anti-rheumatic drug (DMARD) class this drug is considered potent, and associated with a relatively benign side effect profile, iii) the drug has proven efficacy in neurological autoantibody-mediated disorders [[16](#_ENREF_16)]. In choosing mycophenolate, we also recognized that any health benefit obtained from this, comparatively low-cost, treatment would have a better potential to translate into value for money, than if similar benefits were derived from (more expensive) biological drugs.

Most trial participants developed adverse events precluding full dose up-titration. It is unclear whether increased depression, and pain increase reported by three patients reflected true mycophenolate reactions, or fluctuations in the patients’ natural courses. These results suggest utility of an ‘enriched enrolment, randomized withdrawal’ (EERW) design for the conduct of a definite trial, where those patients with troublesome side effect can leave the trial before the randomization phase begins [[17](#_ENREF_17)].

The estimated cost per QALY of £1,875-£4,011 for the mycophenolate-responders is well within the £20,000 cost per QALY threshold recognized by the UK NICE[[18](#_ENREF_18)], providing a first indication that if efficacy can be confirmed, then the intervention may represent value for money.

*Strength:* The study strengths include its prospective nature, independent, concealed randomization, independently-obtained objective markers of skin-sensitivity, and use of a wide range of outcomes. Trial participants’ baseline characteristics were typical for the general population of patients with persistent CRPS[[19](#_ENREF_19)]. The treatment groups were adequately balanced. Inclusion of patients without upper disease duration limit, and swift recruitment over less than 12 months may have reduced ascertainment bias.

*Limitations*: This study was small, and not blinded. Small open studies with few primary events (such as meaningful pain reduction), are at risk of various forms of bias, which have been well described[[20](#_ENREF_20)]. However, unusually for trials in this disease [[11](#_ENREF_11)], half of patients reported meaningful pain relief at some point during the trial, highlighting the case for confirmation in a larger trial. The trial participants had relatively low anxiety and depression values, they took relatively few analgesics, and half of them worked, indicating less distress compared to the general CRPS patient population[[1](#_ENREF_1)]. The observed functional improvements in the drug responders may not extrapolate to a more distressed patient cohort, and we speculate that patients responding to mycophenolate would generally require multidisciplinary support to maximize functional gains. The trial duration was too short to allow an understanding about long-term treatment effects. No routine clinical tests for previously described anti-autonomic autoantibodies are available, and seropositivity was therefore not tested [[4](#_ENREF_4), [22](#_ENREF_22)]. QST results post treatment were available for only one non-responder.

We had chosen a randomised study-design with inclusion of a control group to gauge pain relief from both regression to the mean effects, and natural course over 5.5 months, a duration for which few control-group data exist from randomized trials in this patient group [[11](#_ENREF_11)]. The results of virtually unchanged pain levels in the control group provide preliminary evidence that these design features may have provided no particular advantage over a simple prospective cohort design.

In summary in this randomized, controlled trial of mycophenolate add-on treatment over 5.5 months, a substantial proportion of patients reported meaningful pain reduction on mycophenolate. The study was not designed to clarify the use of mycophenolate in clinical practice and results should not be taken to support the clinical use of this drug. To our knowledge, this is the first study, which has prospectively examined the efficacy of a disease-modifying anti-rheumatic drug (DMARD) in a non-inflammatory chronic pain condition. These promising but preliminary results require confirmation in a larger trial.

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**Conflict of Interest Statement**

The authors declare no conflict of interest with regards to this work.

**Ethical issues**

The trial protocol for this study was registered, Ethics Board approval was obtained, and written informed consent was obtained from each participant

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