Tacrolimus vs. Azathioprine in myasthenia gravis treatment.

A multicenter, prospective, randomized, double blind, head to head clinical trial.

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I would like to express my gratitude to Olga Carmona, who, although not being aware of it, may have helped me find the way.

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1. LIST OF ABREVIATIONS

Ach	Acetylcholine
AchR	Acetylcholine Receptor
Anti-AchR	Acetylcholine Receptor Antibodies
Anti-MuSK	Antibodies to Muscle-Specific receptor tyrosine Kinase
CSR	Complete Stable Remission
DM	Diabetes Mellitus
IVIg	Intravenous immunoglobulin
FK506	Tacrolimus
MG	Myasthenia Gravis
MGFA	Myasthenia Gravis Foundation of America
MGFA-PIS	Myasthenia Gravis Foundation of America Post Intervention Status
MM	Minimal Manifestations
PR	Pharmacological Remission
QMG score	Quantitative Myasthenia Gravis Score

2. ABSTRACT

Current evidences show that tacrolimus could be a good therapeutic option in patients non-responsive to first-line treatments and even it could become one of the first-line drugs for treating MG. Our study will try to determine the effectivity and safety of tacrolimus in 190 myasthenia gravis patients with suboptimal response to azathioprine: after 12 months of treatment they will be randomized to continue with azathioprine or they will be switched to tacrolimus. Patients will follow the allocated treatment during 14 months and the response will be assessed as well as adverse effects.

PURPOSE: To compare azathioprine vs. tacrolimus effectivity and safety in MG patients with suboptimal response to azathioprine at 12 months.

DESIGN: A 14 months multicenter, prospective, randomized, double blind, head to head clinical trial

KEY WORDS: Tacrolimus, Azathioprine, Myasthenia gravis, Clinical trial

3. INTRODUCTION

- **Epidemiology**

  Myasthenia Gravis (MG) is an autoimmune disease due to an alteration in neuromuscular transmission (postsynaptic disorder) that is relatively uncommon. It has a bimodal presentation: the first peak incidence occurs between 15 and 35 years of age, with a clear predominance in women, and a second peak occurs over 50 years in man and 60 years in women (1,2). The annual incidence of MG is 21.27 cases per million people and in people over 60 years the incidence is 60.3 cases per million people (1,3); the prevalence rate is about 20 per 100,000 inhabitants (4).

- **Physiopathology**

  MG is an autoimmune disease, antibodies mediated, against the acetylcholine receptor (AChR), which blocks the receptors in the postsynaptic surface. Because of that acetylcholine is not able to join the postsynaptic receptor and the end-plate potential becomes compromised, reducing the effective synaptic transmission and causing muscle weakness.

Although we know that antibodies production is B-cell-dependant, the way how the immunologic tolerance breakdown occurs it is not well understood. However, T cells role in this disease is becoming increasingly apparent because thymus abnormalities are found in most of MG patients (around 75%) as hyperplasia or thymoma and this is the central organ in T cell-mediated immunity(2).

Anti-AchR antibodies (anti-AchR) cause an impairment of the neuromuscular transmission in different ways:

- B locking the Ach (Acetylcholine) transmission by binding the AchR.
- Decreasing the number of AchR in the neuromuscular junction due to complement-mediated destruction of target receptors.
- Inducing the receptor's endocytosis and consequent destruction.
- Reducing the surface area available for insertion of newly synthesized AchR.

Most of patients are positive for AchR antibodies (range 50-85% of MG) (1,5). Many patients without anti-AchR antibodies have antibodies to muscle-specific tyrosine kinase (anti-MuSK), a membrane protein located in muscular fibres (40-70% of patients without AchR antibodies MG). MuSK antibodies are mainly associated with bulbar presentation and poor prognosis.

As other immunological diseases, MG is frequently associated with other autoimmune disorders as thyroiditis, rheumatoid arthritis or systemic lupus erythematosus.

- **Clinical features**

MG is characterized by fatigability which worsens with exercise and improves with rest, affecting all voluntary muscles. Even though, the most affected are: ocular muscles (diplopia and/or ptosis), bulbar musculature (dysphagia and/or dysarthria), cervical muscles (weakness during neck extension), proximal limb musculature (difficulties in climbing up the stairs and/or manipulate objects over the head) and also respiratory musculature (dyspnea).

To classify the different stages of the disease, the most used is the Myasthenia Gravis Foundation of America (MGFA) Classification which is based on the predominant symptoms and the affectation degree (6,7) (Annex 1).

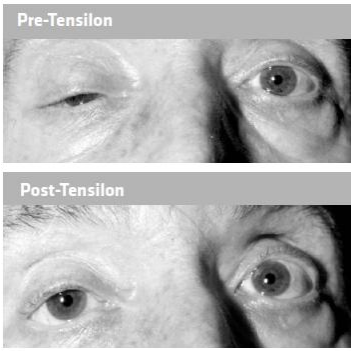
- **Diagnosis** (1,4)

The diagnosis includes clinical, laboratory and electromyographic data:

1. **Clinical presentation**: muscular fatigability which worsens with exercise and improves with rest.
2. **Neurological examination**: to confirm muscle fatigability in different areas such as ocular, shoulder and pelvic girdle and neck muscles. The Quantitative Myasthenia Gravis Score (6) allows us giving a numeric value to weakness which helps on further follow-up visits.
3. **Functional tests**: the objective is to demonstrate an improvement of the fatigability.

   3.1. Tensilon (Edrophonium Chloride) Test: Edrophonium is an acetylcholinesterase inhibitor administered intravenously. It increases the Ach concentration in the neuromuscular junction causing clinical improvement, mainly in the eyelid ptosis and/or extraocular movements.

   3.2. Ice pack Test: it is a non-pharmacological test, available when Edrophonium test is contraindicated. It consists in placing an ice pack over the eye for 2-5 minutes and then assessing for improvement in ptosis.



Ptosis improvement after Tensilon test (1)

4. **Electrophysiological tests**

   - **Repetitive nerve stimulation:** assesses neuromuscular transmission by stimulating the nerve supramaximally at 2-3Hz. A >10% decrement between the first and the fifth evoked muscle action potential is diagnostic for MG.

- **Single- fibre electromyography**: is the most sensitive test of neuromuscular transmission, mainly used in ocular MG. It shows an increased jitter in some muscles, which is an increased time variability between the stimulation and the action potential.

5. Immunological tests

- Anti-AchR antibodies: in 85% of generalized MG are positive whereas only 50% of ocular MG have these antibodies. The concentrations can not be used to predict the severity of disease in individual patients.
- Anti-MuSk antibodies: are present in approximately 40% patients with generalized MG and negative anti-AchR (1,4). They are mainly related to bulbar symptoms and poor prognosis.

  Most of authors consider seronegative MG when both anti-AchR and Anti-Musk are not present (1,4).

- **Management of disease** (based on Catalan Society of Neurology recommendations (1))

  - **Symptomatic treatment with acetylcholinesterase inhibitors**

    Acetylcholinesterase inhibitors are the first–line treatment and the most used is pyridostigmine (Mestinon®) (level U recommendation). It's only a symptomatic treatment because it does not alter the disease progression.

  - **Rapid short-term immunomodulating treatment**: plasmapheresis and intravenous immunoglobulin, mainly used for myasthenic crisis, exacerbations and to prepare symptomatic patients for thymectomy or other surgery (class A evidence).
    - Plasmapheresis: it consists in removing the anti-AchR antibodies from the blood circulation by plasma exchange.
    - Intravenous immunoglobulin (IVIg): it competes with anti-AchR for binding to AchR, decreases the synthesis of anti-AchR antibodies and neutralizes certain pathogenic cytokines.

- **Chronic long-term immunomodulating treatment:** glucocorticoids and other immunosuppressive drugs.
  - Corticosteroids: are considered the current standard for treatment of mild to moderate MG and it is the first line treatment to start with (level B recommendation). Prednisone is generally used when symptoms are not adequately controlled with acetylcholinesterase inhibitors as monotherapy.
  - Azathioprine: is the most widely used long-term immunosuppressant for MG after corticosteroids. It's the first choice steroid-sparing agent in patients with inadequate response to steroids (level B recommendation).
  - Cyclosporine (level A recommendation), cyclophosphamide (level U recommendation) and mycophenolate mofetil (level U recommendation): should be used for patients refractory or intolerant to treatment with steroids and/or azathioprine.
  - Tacrolimus (FK 506): is a macrolide compound which acts on T helper cells to suppress the production of various cytokines (level C recommendation).
  - Etanercept: is a receptor fusion protein which blocks the α-TNF (tumour necrosis factor).
  - Monoclonal antibodies**:** like Rituximab, which is an anti-CD20 drug (level U recommendation).

- **Surgical treatment**: thymectomy is always indicated in patients with thymoma and also in patients anti-AchR positive with generalized myasthenia gravis who are under 55 years old (level C recommendation).

  Surgery is not recommended in anti-MuSK positive patients due to the absence of histological thymus changes in these patients (level U recommendation).

4. BACKGROUND

Azathioprine is considered nowadays the first line immunosuppressant drug used in MG in case of lack of response to corticoids. On the other hand tacrolimus is recommended only when patients are unresponsive to azathioprine, methotrexate or micophenolate mofetil (8).

Azathioprine is an immunosuppressant drug which acts as a purine antagonist by inhibiting DNA synthesis and cell proliferation including lymphocytes and inducing lymphopenia of both B and T cells. It acts through its metabolite 6-mercaptopurine. Azathioprine is used mainly in preventing transplant rejection, rheumatoid arthritis, ulcerative colitis, Crohn's disease and also in myasthenia gravis. One of the most common side effect are flu -like syndrome which occurs after 2 weeks of treatment and sometimes obliges to discontinue the treatment. Other adverse effects are infections, liver toxicity, bone marrow suppression and erythema multiforme (9–11). Moreover, the potential risk of suffering some cancers, especially skin cancer and lymphoma, has to be taken into consideration (2,9–12).

Tacrolimus is also an immunosuppressant drug which acts inhibiting T-cell and IL-2 production. The main mechanism of action of tacrolimus consists on inhibiting the calcineurin phosphatase which reduces the cytokines production. The most frequent adverse effects are mild elevation of serum creatinine, hypertension, headache, diabetogenic side effects, tremor, hyperpotasemia, paresthesia, decreased lymphocyte counts, and raised neutrophil counts. It may also increase the risk of malignancy(11–14).

As other immunosuppressant drugs, tacrolimus and azathioprine side effects are dose dependent and treatment duration dependent (10,13).

One of the disadvantages of azathioprine is the late onset of therapeutic response which is usually delayed to 4-12 months, obtaining the maximal effect after 12-24 months of treatment. Another disadvantage is that in patients who are previously treated with allopurinol it should be kept on mind to reduce the azathioprine dosage and monitor the drug blood levels; because of that azathioprine is not the best immunosuppressive drug in people who needs to be treated with allopurinol.

On the other hand, tacrolimus effect is evident after only 1 month of treatment (15,16) and even some studies show that FK506 (Tacrolimus) is significantly effective only 2 weeks after the administration (17). Ponseti et al. (16) concluded in their article that 9/13 patients evaluated achieved pharmacological remission (no symptoms during one year, except ocular fatigability) during the first month of treatment and all patients reached the endpoint at 12 months; other findings of the same study were that the Quantitative Myasthenia Gravis Score (QMG score) and the AchR antibodies titles decreased and the dose of prednisolone could be reduced and withdrawn in all patients; moreover, the dose of tacrolimus could be reduced during the 12 months of follow-up. The main limitation of this study was that it was a non-blinded nor randomized study with small number or participants (13 patients).

In the same line, Nagaishi et al. (15) concluded in their cohort that, as tacrolimus needs a short period of time to start its effectivity, it is possible to start cutting down the glucocorticoids dose only one month after being started the treatment. To summarize, in their report 5 /10 patients achieved pharmacological remission or minimal manifestations, being possible to withdraw the corticoids in 4 of those 5. Even tacrolimus was slowly tapered off in 2 patients without exacerbations.

Moreover, another group composed by Zhao et al. (18) showed that clinical improvement was evident from the fourth week of treatment and even increased during the follow-up; in their patients it was also possible to decrease the glucocorticoids dosage in 15/43 participants at 12 week and 23/43 at 24 week. In this study patients not only demonstrated improvement in muscular strength, but also showed less fatigability and had better scores in quality of life.

In addition, there is another retrospective, non-randomized and non-controlled study performed by Ponseti and colleagues (19) where low dose of tacrolimus (0.1mg/kg/day) was administered to 212 patients during 5 years. Corticoids dosage was started to be reduced after 15 days of beginning tacrolimus administration and, if possible, were withdrawn during the follow-up: they were withdrawn in 91.6% of patients after the first year and in 95.1% at the end of the study. It was observed that, among thymectomized patients, before cyclosporine and prednisone dependent and

during the study treated with corticoids and tacrolimus, complete stable remission (CSR) was achieved in 5.7% of the cases, pharmacological remission (PR) in 76.9% and minimal manifestations (MM) in 6.6% of the patients. The investigators also concluded that there was a relationship between the thymus pathology and the probability of reaching CSR at 5 years after operation. Concerning to the group treated with prednisone and azathioprine after 24 hours post-thymectomy, 80.8% of patients with hyperplasia reached CSR, 48.1% in those with thymic involution and only 9% in those with thymoma. Furthermore, changes in muscular strength were evident after the first week of treatment in 8% of the patients, after 1 month in 50%, after 3 months in 80% and in 99% at the end of the study.

The same authors showed in other article (Ponseti et al. (20)) that early post-thymectomy administration of prednisone combined with tacrolimus (0.1 mg/kg/day) (39 patients) was more effective to achieve CSR than steroids alone(1.5 mg/kg/day) (40 patients). CSR was obtained in 47.5% of the patients who received combined treatment versus the 41% obtained in the prednisone group. Furthermore, CSR was obtained in a shorter period of time in the first group (median follow-up to achieve CSR of 38.2 months in the combined treatment group versus 64.6 months in the monotherapy group). They suggested that tacrolimus could be a good option of early treatment in post-thymectomy period (the treatment was started 24 hours after the surgery) being able to achieve better long-term responses and the probability of achieve CSR (19,20).

With regard to the optimal timing to start with tacrolimus, the early stages of disease seems to be related with the positive response to calcineurin inhibitors treatment as tacrolimus. Moreover, patients with MG and thymoma could respond better to tacrolimus (21).

Tacrolimus has only been investigated as monotherapy (without glucocorticoids) in ocular MG in a short series of patients and in a case-report of generalized MG, suggesting to be effective; Yagi et al. (8) described their experience with 4 patients with ocular MG who received only tacrolimus for 2 years: during this period of time AchR titles decreased in the four patients and all of them remained clinically stable

without remarkable adverse effects. Controlled trials are needed to confirm this observation. Evoli et al. (22) administered tacrolimus to a patient with generalized MG in which other immunosuppressant drugs were contraindicated and the patient achieved PR after 14 months of treatment.

Taking into account the safety of treatments, tacrolimus seems to be a reliable option for MG in recommended doses for the disease (3 mg/day) (23–25), which are low in comparison with those used for organ transplantation (0.075-0.30 mg/kg/day). This dose has proved to be effective and safe for treating MG in previous studies (17,26).

There are several studies approaching tacrolimus security. Konishi et al. (26) presented the results of a 2 years follow-up study in which no serious side-effects, like Diabetes mellitus (DM) or renal toxicity, were shown. Minor adverse effects were reported in 66% of the patients but they could be solved by discontinuation of tacrolimus during 48 hours or without any specific measures; only 33% of the patients suffered an increased neutrophil count and decreased lymphocyte count.

Carrying on with treatment security, Zhao et al. (18) concluded that tacrolimus seems to have a good security profile; the majority of side effects were experienced temporarily and many patients reported being free from adverse events at the end of the study (24 weeks). Although hyperglycaemia or diabetes mellitus (DM) are reported as tacrolimus side-effects, tacrolimus was given to a patient with type 2 DM and only it was necessary increasing the doses of hypoglycemiant drug to control the pre-existing DM (22), which suggests that suffering DM is not a contraindication for taking tacrolimus.

Ponseti et al. (16) reported three cases of solid tumors during their study. However, they were unlikely to be due to tacrolimus because they appeared in a short period of time after being started the treatment.

Tacrolimus can be also a good option instead of azathioprine in case of patients who need to take Allopurinol because of drug interaction with azathioprine. Allopurinol inhibits the enzyme xanthine oxidase and consequently hampers the conversion of

azathioprine into 6-thiouric acid, which accumulates and this can lead to bone-marrow suppression (2).

One of the more recent studies related to the treatment of MG with tacrolimus is a randomised, double blind, placebo-controlled study performed during 28 weeks; patients who were receiving prednisolone at doses equivalent to 10-20mg/day were divided into two groups to compare taking prednisolone and placebo versus prednisolone and tacrolimus while trying to reduce the glucocorticoids dosage. The results demonstrated that tacrolimus may have a steroid-sparing effect which allowed the corticoids dosage to be decreased during at least 28 weeks and confirmed its safety and tolerability. A larger and longer study is required in which initial glucocorticoids dose should be the minimum to control symptoms for being able to detect a clearer difference between tacrolimus and placebo (24).

A similar study, also performed in Japan, tried to determine the effect of tacrolimus (3mg/day) in combination with low doses of prednisolone (not exceeding 20mg/day and tapering the glucocorticoids dose to the minimal to maintain MM) versus corticoids in monotherapy, in de novo MG patients during 1 year. The early-phase treatment consisted on giving oral prednisolone (<20mg/day) and if it was needed plasmapheresis and/or high-dose intravenous methylprednisolone; this phase ended when patients remained in MM state taking ≤10mg/day of prednisolone. Tacrolimus group of treatment was related to a shorter duration of the early phase, lower requirements of intravenous methylprednisolone or plasmapheresis and to the possibility of corticoids reduction. In terms of safety, no severe side effects were observed during this year (23).

RATIONALE FOR THE STUDY

Taking into account the information available until nowadays, a large**,** double-blind, randomized and controlled clinical trial is required to determine definitive evidence for the use of tacrolimus as a treatment of Myasthenia Gravis and the best indication for its use.

This clinical trial would allow us to:

- Compare directly time-response between azathioprine and tacrolimus.
- Confirm the superiority of tacrolimus as steroid-sparing effect, avoiding long term corticoids side effects.
- Compare side effects of both treatments.
- Confirm long-term security of tacrolimus at low doses (3mg/day).

5. HYPOTHESIS AND OBJECTIVES

○ Hypothesis

1) Switching to tacrolimus is more effective than continuing the treatment with azathioprine in patients with suboptimal response at 12 months of treatment.

2) Tacrolimus is as safe as azathioprine in patients with myasthenia gravis over a period of 14 months.

3) Tacrolimus time of response is shorter than azathioprine in myasthenia gravis treatment.

○ Objectives

- **Main objective**

  To assess tacrolimus superiority respect to azathioprine in suboptimal responders to first-line treatment (azathioprine) defined as lack of clinical control or impossibility of reducing the corticoids dose below 30mg every other day after 12 months of treatment.

- **Secondary objectives**

  - To evaluate tacrolimus safety as MG treatment comparing it with azathioprine.
  - To define the tacrolimus time of response in myasthenia gravis patients.

6. METHODOLOGY

6.1. Study design

A multicenter, prospective, randomized, double blind, head to head clinical trial to compare azathioprine vs. tacrolimus in MG patients with suboptimal response to azathioprine at 12 months.

6.2. Study population

- **Inclusion criteria**
  - Patients aged from 18 to 60 years with generalized myasthenia gravis able to sign the informed consent
  - Suboptimal response to azathioprine, defined as: lack of clinical control or impossibility of reducing the corticoids dose below 30mg every other day after 12 months of treatment.

- **Exclusion criteria**
  - Patients who have received other immunosuppressant treatment than azathioprine and corticoids prior to the administration of tacrolimus.
  - Pregnant and breastfeeding women
  - Uncontrolled hypertension
  - Renal failure defined as Glomerular Filtration Rate < 60 ml/min/1,73 m^2
  - Persistent dysfunction of liver
  - Concomitant infection
  - Clinical immunodeficiency syndrome
  - Malignant tumour
  - Previous allergy to tacrolimus
  - Weight under 50 kg or over 80 kg

- **Sample size**

  The estimated sample size is 190 patients, divided into two groups of 95: one will receive tacrolimus and the other azathioprine.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 95 exposed subjects and 95 in the non-exposed are necessary to recognize as statistically significant a relative risk greater than or equal to 2.2. A proportion in the non-exposed group has been estimated to be 0.2. It has been anticipated a drop-out rate of 30%. The Poisson approximation has been used.

It is expected a 20% of response (response measured as a drop in the QMG score of ≥4 points) in azathioprine group due to the fact that the data published revealed a slight clinical status improvement between 12 and 24 months of treatment, although the mean peak is estimated to be at 14 months (27,28).

The minimum Relative Risk estimated is 2.2 since the minimum available data of tacrolimus responders is 44%, which is expected to be the lowest difference to detected (29)**.**

- **Sampling**

Consecutive sampling (Non-Probability Sampling): this technique consists on collecting all available subjects that attend to the hospital and meet the criteria as part of the sample. It is the most convenient method taking into account that MG is a low-prevalence disease.

- **Setting**

Multicenter study including all centers of Catalonia with a neuromuscular disease department: Hospital Clínic (Barcelona), Hospital Universitari de Bellvitge (Barcelona), Hospital de Sant Pau (Barcelona), Hospital del Mar (Barcelona), Hopital de Vall d'Hebrón (Barcelona), Hospital Universitari Germans Trias I Pujol (Badalona), Hospital Parc Taulí (Sabadell), Hospital Josep Trueta (Girona), Hospital Arnau de Vilanova (Lleida) and Hospital Joan XXIII (Tarragona).

- **Estimated time of recruitment**

The time estimated is 2.5 years (30 months) although it is extensible to the time required to recruit all the patients needed.

Bearing in mind that a competitive recruitment between centers will be performed, the recruitment period will end when the 190 patients required will be included.

The duration has been estimated taking into account that in Catalonia there are 161 new MG cases reported each year; 75% of those will not be controlled with corticoids therapy and will receive azathioprine. Bearing in mind that 50% of azathioprine patients will not respond to this drug, 60 patients will be susceptible to participate in the clinical trial every year. It should also be considered that in Catalonia there are around 1,400 patients diagnosed of MG, those a large number of them are currently treated with azathioprine and will not respond optimally to the treatment after 12 months; these patients also will have the chance to participate in the study.

- **Randomization procedures**

The patients will be divided into two groups with a randomized electronic procedure: one group will continue azathioprine treatment and the other group will switch to tacrolimus.

Adjustment factors for dynamic allocation in randomization (24):

- Prednisolone dose at baseline (<15 or ≥15 mg/day)
- Past history of thymectomy or non-thymectomy
- Time elapsed after thymectomy (< or ≥ 1 year)
- Thymic histology

6.3. Study treatment

a) **Study treatment groups**

Oral tacrolimus will be administered to one group of patients at a daily dose of 3 mg (1 mg of tacrolimus in the morning and 2 mg in the evening) 2 hours after the meal to ensure the maximum absorption.

The other group will receive 150 mg/day oral azathioprine in one single dose in the morning.

b) **Other treatments**

- Glucocorticoids

Prednisolone dose reduction will be able to be tried after 15 days of being started the clinical trial as investigator criteria. The daily dose will be decreased 10 mg/day every 4 weeks.

The dose will be tried to be reduced in case of maintenance of Minimal Manifestations status based on MGFA Post Intervention Status (Annex 1).

However, if the symptoms worsen and MM status is not maintained, the prednisolone dose will be immediately increased until recovery and achieve a stabilised MM status. After that, the prednisolone could be once again reduced.

In case of prednisolone could be stopped, the study treatment (tacrolimus vs. Azathioprine) will be maintained until the end of the study.

- Cholinesterase inhibitor: The dose of pyridostigmine should be optimized before entering in the clinical trial because the dose is not allowed to be changed due to it could influence the results, except in the interest of patient safety (30).

- Other MG therapies apart from tacrolimus, azathioprine, prednisolone and pyridostigmine are not allowed during the study such as thymectomy, radiotherapy, other immunosuppressive treatments, plasmapheresis, intravenous immunoglobulin or monoclonal antibodies.

c) **Treatment duration**

The study will be performed during 14 months in order to be able to observe the maximum effect of both drugs which is contained in this interval of time.

d) **Subjects removal/withdrawal**

The subjects will be removed from the clinical trial in case:

- Any adverse event that could be related to study drug under investigator criteria.

- In case the patient needs some extra medication that is not allowed in this study.
- At any time that participant retires the informed consent.

6.4. Study variables and requirements

- **Independent variable**
  - Drug administered as a main immunosuppressant treatment: azathioprine or tacrolimus

    It will be measured as a dichotomous nominal qualitative variable.

    The drug doses will also be recorded and it will be performed a descriptive analysis with this data.

- **Dependent variables**
  - Quantitative MG score for Disease Severity (QMG score): is a discrete quantitative variable which can adopt values from 0 to 39 points. In this scale there are assessed several items (each rated 0 to 3) corresponding to sentinel muscle groups including arm strength, leg strength, face and neck muscle performance, swallowing, grip strength, forced respiration and gaze impairment. The test result gives an idea of the MG severity degree.

    This is the recommended scale for the Task Force of the Medical Scientific Advisory Board of the MGFA to be used in all prospective studies of therapy for MG.

    Equipment requirements: calibrated spirometer, stopwatch, cups and water for swallowing tests, goniometer and dynamometer.

    Patients should not have taken any acetylcholinesterase inhibitor for 12 hours prior to the test if they are receiving this treatment and it is considered safe from a medical point of view.

    A drop in the QMG score of ≥4 points will be considered a clinical improvement (31) .

    This variable will be considered the main variable for measuring treatment effectivity.

- MGFA post intervention status (MGFA-PIS) → it will be measured following the Myasthenia Gravis Foundation of America (MGFA) criteria (annex 1). This scale was made to assess the clinical status of MG patients after the treatment instauration. It is a nominal qualitative variable composed of the following categories:

  - **Status observed** in each assessment (it must be chosen only one of the following categories):
    - CSR (Complete Stable Remission): this will not be evaluated taking into account the study characteristics.
    - PR (Pharmacologic remission)
    - MM (minimal manifestations): from MM-0 to MM-3
  - This classification also consider **change in status**:
    - I (improved)
    - U (unchanged)
    - W (worse)
    - E (exacerbation)
    - D of MG (Died of MG)

- Glucocorticoids withdrawal: is a nominal qualitative variable which will be registered as: glucocorticoids withdrawn, glucocorticoids < 10mg every other day or glucocorticoids ≥10mg every other day. It also be recorded the glucocorticoids dosage in mg/day and a descriptive analysis will be performed with this data.

  It is an indirect measurement of the efficacy of the treatment because if the main immunosuppressant treatment is effective it will be possible to reduce the corticoids dosage.

Treatment effectiveness will be considered when:

- A drop of 4 or more points in the QMG score and/or
- PR or MM is achieved in the MGFA-PIS and/or
- Glucocorticoids are able to be withdrawn or the dose is < 10mg every other day.

Effectivity will be measured principally with the QMG score and secondly with the MGFA-PIS scale and glucocorticoids withdrawal/dosage under 10 mg every other day.

The treatment will not be considered clinically effective whether the clinical status changes but from pharmacological remission to minimal manifestations representing a worsening of the patient status.

- **OTHER VARIABLES:** these variables will be only recorded (descriptive analysis) and it will not be performed a statistical analysis using this data.
    - MGFA clinical classification (annex 1): is a scale made by the MGFA in which the patients are classified into different subgroups depending on the clinical features as ocular or generalized affection and its degree of severity. It is an ordinal qualitative variable that can accept values from I to V (from less severe to more severe). Changes in this scale can imply a clinical improvement or worsening.
    - MG-Activities of Daily Living (MG-ADL): is a scale for assessing the capacity to perform different activities of daily living as talking, chewing, swallowing, breathing, brushing the teeth/combing the hair or arising from the chair and it is also assessed the double vision and eyelid drop. It is a discrete quantitative variable in which the 8 items are rated from 0 to 3 and the total score can point from 0 to 24, the higher the more impairment.

      There is no need of any equipment or training. It is a patient reported questionnaire that can be filled in only 2-3 minutes.
    - Anti-AchR antibodies titre: is a continuous quantitative variable which measures de blood antibodies concentration. It will be assessed through blood tests that will be performed periodically during the clinical trial and the results will be presented in mmol/L. There is no clear evidence of the correlation between antibodies titre and disease activity, reason to collect this data in order to try to draw a conclusion from it.

- Adverse effects: all the adverse effects observed during the clinical trial will be recollected and it will be performed a descriptive analysis. The adverse events can be communicated directly by the patients or observed during the periodic assessments. Any event appeared after azathioprine or tacrolimus administration will be considered to be caused by the medical treatment.

  We will consider Serious Adverse Event in case of threatening life condition or need of hospitalization and it should be communicated in less of 24 hours**.**

- **Covariates:** these variables will be collected in order to avoid confusion as they can act as confusion factors and alter the interpretation of the results.
  - Sex: is a dichotomous nominal qualitative variable: male or female.
  - Age: is a discrete quantitative variable and will be expressed in years.
  - Previous thymectomy: is a dichotomous nominal qualitative variable and will be expressed as thymectomized patients or not thymectomized patients.
  - Time elapsed from thymectomy: is a discrete quantitative variable and will be measured in years.
  - Type of thymus pathology observed after thymectomy: It is a qualitative variable and it will be registered as: thymic hyperplasia, thymoma, thymic involution or normal thymus.
  - Pyridostigmine concomitant treatment and its dose: it will be registered as a dichotomous qualitative variable (yes or no) and it will also be treated as a discrete quantitative variable and it will be expressed in mg/day.
  - Antibodies anti-MuSK: is a continuous quantitative variable and will be measured in mmol/L.
  - Disease duration from the diagnosis: it is a discrete quantitative variable and will be expressed in years.

- Age at onset: it is a discrete quantitative variable and will be expressed in years.

6.5. Assessment and safety monitoring

After the onset of treatment several controls should be done to assess the efficacy and the safety of the administered medication.

Clinical assessment should be performed at baseline, every 2 weeks during the eight first weeks and after that once a month until the endpoint of the clinical trial.

Each assessment will consist of:

- Anamnesis and physical examination
- Functional tests (performing them at least 8 h after anticholinesterase administration to prevent any influence in the results):
  - MGFA clinical classification
  - MGFA post-intervention status
  - MG-Activity of Daily Living Profile
  - Quantitative MG Score
- Vital signs (Blood pressure and heart frequency) and weight.
- ECG
- Laboratory tests:
  - Complete Blood Count
  - Liver Function Test (LFT)
  - Renal Function
  - Electrolytes
  - Basal glucose
  - Cholesterol (Total, HDL and LDL)
  - Serum anti-AchR antibodies level (measured by radioimmunoassay).
- Concomitant medication (recorded by patients on each day in mg/day):
  - Prednisone (in case the patient received prednisolone on alternate days it will be converted to a mean daily dose).
  - Pyridostigmine

- Other drugs administered during the study

- Adverse effects and complications: unfavourable events occurring after the study drug administration will be considered possibly related to this drug (Annex 2).

  In case of side effects, the responsible investigator will be able to decide:

  - Treating them whether there is some treatment available.
  - Temporary discontinuation of the drug
  - Drug discontinuation

  To maintain the blindness and avoid a procedure bias due to characteristic side effects of each drug, two investigators in each center will perform the assessment visits: one for performing the functional test blinded to adverse events and the principal investigator for assessing adverse events and compliance.

6.6. Statistical analysis

- **Descriptive analysis**

  Quantitative continuous variables will be measured as means +/- standard deviation (SD) as appropriate and categorical variables will be presented as percentages in each group.

  Efficacy endpoints will be given as percentages in each group of treatment.

- **Bivariate analysis**

  Considering that the treatment administered is a nominal qualitative outcome, the chi square test will be performed to determine the differences between groups to evaluate qualitative variables and the U-Mann-Whitney test will be applied in case of discrete and continuous quantitative variables.

- **Multivariate analysis**

  A multivariate analysis will be performed adjusting for co-variables to avoid confusion caused by the effect of other variables on the effect of the treatment.

In this study a Cox's regression model will be performed to describe the relationship between the analysed variables because with this model the time to reach the endpoint is taken into account.

As a measure of association, hazard ratio will be calculated to estimate the risk of the different groups.

All statistical analysis will be carried out with the Statistical Package for Social Science (SPSS), version 19.0.

Statistical significance will be considered at a p value <0.05.

6.7. Study limitations

- Due to myasthenia gravis is a relatively low-prevalent disease it will take time to achieve the estimated sample size and, furthermore, to collect the subpopulation of patients with suboptimal response to azathioprine. To minimize this restraint it will be done a multicenter study and, in this way, it will be easier and faster collect all the patients that are needed.

- As it is a clinical trial, by definition it is a high cost to perform the study, more than other type of studies but this is the best design to try to answer the questions previously set out.

- It should be considered that this is a prospective study and for this reason lost to follow-up participants will take place due to side-effects, non-compliance of the treatment or simply by their own will; it should not be a problem because we have taken it into account when calculating the sample.

- Even it is a double-blind clinical trial, side-effects that are characteristic from one drug or the other can impair the blinding process and induce a procedure bias. To avoid this item two investigators in each center will be encharched to the assessment visits: one for performing the functional test blinded to adverse events and the principal investigator for assessing adverse events and compliance.

- The efficacy will be measured through different tests that have been approved and are recommended for testing myasthenia gravis status, but it should be admitted that the results can vary depending on the neurologist involved. To minimize this subjectivity all neurologist will be trained in the same way to perform the tests to achieve the most homogeneous results.

- The patients enrolled in the study will have different characteristics apart from having the same disease and share the inclusion and exclusion criteria due this is a low-prevalence disease and to achieve all the people needed it would be very difficult to narrow more the sample criteria to homogenize the sample. It will be performed a multivariate analysis to adjust for the different variables that could act as a confusion factor.

- To maintain the blindness all patients will receive a fixed dosage; because of that we have restricted participants inclusion to weight range between 50 and 80 kg.

7. ETHICAL ASPECTS

This clinical trial will follow the medical ethics requirements defined on the Declaration Of Helsinki involving Ethical Principles for Medical Research Involving Human subjects (last actualization October 2013).

It must be approved by the Clinical Research Ethics Committee (CEIC) of every centre participating in the study for being able to be performed.

The research project will be performed in agreement with the legal framework related to clinical trials: "Ley 29/2006 de 26 de Julio, de garantías y uso racional de los medicamentos y productos sanitarios" and "RD 223/2004 de 6 de febrero: ensayos clínicos con medicamentos".

This trial will be registered in AEMPS webpage with the EudraCT application.

All the information obtained will be confidential and the anonymity of the patients will be guaranteed according to the "Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal".

All the patients must be properly informed and sign the informed consent sheet (Annex 3) before taking part of the project.

Every investigator will have to declare no conflict of interests.

In this clinical trial ethics principles are respected because the new treatment, tacrolimus, is compared to the current first-line treatment, azathioprine. A placebo treatment arm to compare the treatment with would not be ethical and, thereby, preventing one group of being correctly treated.

Taking into account azathioprine maximal effect occurs after approximately 24 months of treatment at the latest, the duration of the clinical trial should be adjusted at 14 months. We should remember that patients who are treated with azathioprine will have already been receiving this drug during 1 year before participating in the clinical trial. Bearing in mind this data, within 14 months of study it will be possible to assess azathioprine effectiveness. In case of non optimal response in some patients, azathioprine will be switched to another drug because it would not be ethical continuing with a treatment that has been proved not being effective.

8. WORKING PLAN AND CHRONOGRAM

The study will be completed in 5 years and the organization of the different phases will be:

1. Preparation of the project (*It will be performed by the steering committee: composed by 3 investigators*):

   1.1. Drafting of the protocol (1 month)

   1.2. Coordination of the centres and members of the study (3months). It includes:

   - Selection of the centres involved and principal investigators of each center.
   - Identification of problems and elaboration of the definitive protocol.

   The steering committee will be in charge to coordinate these activities and will organize an investigator's meeting will all the neurologists involved in the trial. In this meeting will take place the training of the neurologists to perform the patient's evaluation minimizing inter-observer variability and discuss possible problems.

   1.3. Ethics committee approval of each center (simultaneously to 1.2)

2. Sample collection (30 months): patients will be collected in order of appearance and randomized distributed into the different study groups. Inclusion period previewed will be 2.5 years (it can be prolonged in case of not achieving the predefined sample). (*It will be performed by all the investigators of each center enrolled in the study and the survey monitor).*

3. Follow-up visits and data collection: 14 months. The clinical assessment will be performed *(It will be performed by all the investigators of each center enrolled in the study and the survey monitor):*

   3.1. The first visit before receiving the treatment (it includes the collection of personal and baseline data).

   3.2. One visit each 2 weeks during the following 8 weeks.

3.3. One visit once a month until the endpoint of the study.

Periodic investigators meeting will be planned to coordinate the clinical trial and the project evolution.

The data collection will electronic centralized: the “survey monitor” will be encharged of assessment of reliability of data.

4. Statistical analysis and results (3 months). *(Steering Committee + Statistician)*

5. Drafting of the final report, dissemination of the results and redaction of scientific articles (3 months). *(Steering Committee)*

This is the standard planning for each patient but as the patients will be collected consecutively each patient will enter to the study at a different time. Taking into account this, the clinical trial will lasts approximately 4.5years (54 months) due to:

- Preparation of the study: 4 months
- Collection of all the patients including treatment of the last patient recruited: 2.5years (30 months) + 14 months.
- Statistical analysis and spreading of the results: 6 months.

CHRONOGRAM SCHEME

Time period

		Year 1				Year 2	Year 3	Year 4	Year 5	
	Months	1-3	4-6	7-9	10-12				1-3	4-6
ACTIVITIES	1. Drafting of the protocol									
	2. Coordination of the centres and members of the study + definitive protocol									
	3. Ethics committee approval									
	4. Sample collection + treatment + follow-up visits									
	5. Statistical analysis and results									
	6. Final report, dissemination of the results and redaction of scientific articles.									

9. BUDGET

	Cost	Nº of persons	Time/Nº	Total
STAFF				
- Steering committee	1,500€/year	3	4.5 years	20,250€
- Monitor survey (partial time work)	9,000€/year	1	2.5 years	22,500€
- Investigators[1]	50€/each visit	2	17 visits x 190 patients	161,500€
- Statistician	35€/hour	1	60 hours	2,100€
	Cost patient/month	**Nº of patients**	**Time**	**Total**
Drugs				
- Tacrolimus (PVL)	69.12€	95	14 months	91,929.60€
- Azathioprine (PVL)	10.40€	95	14 months	13,837,32€
	Cost/visit	**Nº of visits**	**Nº of patients**	**Total**
Assessment				
- Laboratory tests	70€	17	190	226,100€
- Electrocardiogram	18€	17	190	58,140€
	Cost	**Nº**	**Nº persons**	**Total**
Publications				
Neurology	1.500€	1	---	1,500€
Meetings				
	70€/person	3	30	6,300€
Congress				
AAN[2]	6,000€	1	3	18,000€
			TOTAL	**622,156.92€**

[1] Each visit should be performed by 2 different investigators and it will be paid globally at 50€ each visit.
[2] American Academy of Neurology (AAN)

10. ANNEXES

10.1. ANNEX 1 : FUNCTIONAL TESTS

Table 1. Quantitative MG Score for Disease Severity (7)					
Tests Item	None	Mild	Moderate	Severe	Score
Grade	0	1	2	3	
Double vision on lateral Gaze on right or left (circle one), seconds	61	11-60	1-10	Spontaneous	
Ptosis (upward gaze), seconds	61	11-60	1-10	Spontaneous	
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing 4 oz water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing/chokin g or nasal regurgitation	Cannot swallow (test not attempted)	
Speech after counting aloud from 1 to 50 (onset of Dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9	
Right arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9	
Left arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9	
Vital capacity, % predicted	≥80	65-79	50-64	<50	
Rt-hand grip, kgW					
Men	≥45	15-44	5-14	0-4	
Women	≥30	10-29	5-9	0-4	
Lt-hand grip, kgW					
Men	≥35	15-34	5-14	0-4	
Women	≥25	10-24	5-9	0-4	
Head lifted (45 degrees supine), seconds	120	30-19	1-29	0	
Right leg outstretched (4 degrees supine), seconds	100	31-99	1-30	0	
Left leg outstretched (4 degrees supine), seconds	100	31-99	1-30	0	
				TOTAL QMG SCORE (RANGE, 0-39):	_____

Table 2. MG Activities of Daily Living (MG-ADL) Profile (32)					
Grade	0	1	2	3	Score
1. Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. Impairment of ability to brush	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				TOTAL MG-ADL score (RANGE, 0-24):	_____

Table 4. MGFA Postintervention Status (7)	
Complete Stable Remission (CSR)	The patient has no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eye closure is accepted.
Pharmacological Remission (PR)	The same criteria as for CSR except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal Manifestations (MM)	The patient has no symptoms or functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least [1 year]. The duration of post-intervention status of outcome is left to the discretion of the Investigator, but should be predetermined.
MM-1	The patient continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy
MM-2	The patient has received only low dose cholinesterase inhibitors (< 120 mg pyridostigmine per day), for at least [1 year]. The duration of post-intervention status of outcome is left to the discretion of the Investigator, but should be predetermined.
MM-3	Patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.
Change in Status	
Improved (I)	A substantial decrease in pre-treatment clinical manifestations or a sustained substantial reductions in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in a predetermined quantitative score, if the patient has not met minimal manifestations or better.
Unchanged (U)	No substantial change in pre-treatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in a predetermined quantitative score, if the patient has not met minimal manifestations or better.
Worse (W)	A substantial increase in pre-treatment clinical manifestations or a substantial increase in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in a predetermined quantitative score.
Exacerbation (E)	Patients who have fulfilled criteria for CSR, PR, or MM but subsequently developed clinical findings greater than permitted by these criteria. In prospective studies, this should be defined in terms of a change in a predetermined quantitative score.
Died of MG (D of MG)	Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy. List the cause.

Table 3. MGFA Clinical Classification (7)		
Class I	Any **ocular muscle** weakness May have weakness of eye closure All other muscle strength is normal	
Class II	**Mild** weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity	
	IIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement in oropharyngeal muscles
	IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class III	**Moderate** weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity	
	IIIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement in oropharyngeal muscles
	IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class IV	**Severe** weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity	
	Iva	Predominantly affecting limb, axial muscles, or both May also have lesser involvement in oropharyngeal muscles
	IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class V	Defined by **intubation**, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb	

10.2. ANNEX 2: SIDE EFFECTS

TACROLIMUS: MOST FREQUENT ADVERSE EVENTS (13)	
Cardiac	Tachycardia, ischemia
Hematologic	Anaemia, leucopoenia, thrombocytopenia, leucocytosis
Neurologic	Tremor, headache, seizures, altered level of consciousness, paresthesia or dysesthesia, dizziness, peripheral neuropathies
Ocular	Blurred vision, photophobia
Ear alteration	Tinnitus
Respiratory	Dyspnea, pleural effusion, pharyngites, nasal congestion
Gastrointestinal	Diarrhoea, nausea, bowel inflammation, ulcers, vomit, constipation, abdominal pain
Renal	Renal failure, toxic nephropathy, bladder symptoms
Dermatologic	Itching, rash, alopecia, acne, hyperhidrosis
Musculoskeletal	Arthralgia, muscle cramps, limb pain, back pain
Metabolic and nutritional	Hyperglycaemia, Diabetes Mellitus, Hyperpotasemia, Hypomagnesaemia, hypophosphataemia, hyperpotasemia, hypocalcaemia, hyponatraemia, fluid retention, hyperuricaemia, anorexia, metabolic acidosis, hyperlipidaemia
Vascular	Hypertension, haemorrhage, thromboembolism, ischemic episodes
General	Asthenia, fever, malaise, increased weight
Hepato-biliary	Hepatic enzyme alteration, cholestasis, jaundice, hepatitis, cholangitis
Psychiatric	Insomnia, anxiety, confusion, depression, mood changes, nightmares, hallucinations
Immunologic	Allergic reactions

* Although it is not very frequent, infections or tumours can appear as in other immunosuppressant treatments.

AZATHIOPRINE: MOST FREQUENT ADVERSE EVENTS (10)	
Hematologic	Bone marrow suppression, leucopoenia, thrombocytopenia
Gastrointestinal	Nausea
Immunologic	Infections, hypersensitivity reactions

* Although it is not very frequent tumours can appear as in other immunosuppressant treatments.

* Characteristic adverse events: pancreatitis, cholestasis, impaired liver function.

10.3. ANNEX 3: INFORMATION SHEET AND INFORMED CONSENT

FULL D'INFORMACIÓ PELS PACIENTS

1. Finalitat de l'estudi

La miastènia gravis és una malaltia neuromuscular autoimmune, motiu pel qual el seu principal tractament són els fàrmacs immunosupressors. Actualment el fàrmac considerat de primera elecció és l'azatioprina, amb o sense glucocorticoides i/o piridostigmina com a tractaments coadjuvants si es consideren necessaris per controlar la simptomatologia derivada de la malaltia. L'azatioprina té com a desavantatge principal el seu lent inici d'acció, que es pot observar entre els 4 i 12 mesos. A més, el seu efecte màxim es pot retardar entre 1 i 2 anys des del inici del tractament. Això fa necessari la presa de corticoides com a tractament coadjuvant tot aquest temps, sense possibilitat de reduir-ne la seva dosi, amb tots els efectes adversos que comporta la presa de glucocorticoides durant un període llarg de temps.

Actualment s'està investigant el tractament amb tacrolimus, un altre immunosupressor que, tot i no ser un fàrmac nou ja que s'usa en altres patologies, és d'ús recent i experimental en el camp de la miastènia gravis. Segons l'evidència basada en estudis previs publicats, el tacrolimus té un inici d'efecte terapèutic més ràpid ja que la millora clínica s'ha documentat entre les 2 i 4 setmanes. Per aquest motiu la presa d'aquest fàrmac suposa un avantatge respecte la presa d'azatioprina ja que podria esdevenir un fàrmac alternatiu en pacients no responedors a l'azatioprina i, fins i tot, podria convertir-se en el tractament immunosupressor de primera línia al tenir una resposta tan ràpida. Això permetria la reducció precoç dels tractaments concomitants com els glucocorticoides, evitant els efectes adversos de la seva presa a llarg termini.

Aquest estudi pretén ser una referència per considerar el tacrolimus un tractament eficaç i segur de la miastènia gravis i, fins i tot, ser instaurat com a tractament de primera línia.

2. Descripció del procés

Es tracta d'un assaig clínic en què s'administrarà aleatòriament un dels dos fàrmacs, azatioprina o tacrolimus, en pacients amb resposta subòptima a l'azatioprina després d'un període de 12 mesos de tractament. Al ser un procés aleatoritzat, tot els pacients tenen les mateixes probabilitats de rebre un tractament o l'altre.

Posteriorment al inici del tractament, caldrà dur a terme revisions i analítiques periòdiques que es realitzaran en el centre de referència.

Durant l'assaig clínic està permès el tractament amb piridostigmina (anticolinèrgic) i/o glucocorticoides tot controlant-ne les dosis administrades i sempre que aquests fàrmacs siguin necessaris per controlar la clínica miastènica.

Els efectes indesitjats més freqüents que es poden patir en el cas de rebre un dels dos tractaments són:

- Nefrotoxicitat
- Hipertensió
- Neurotoxicitat
- Intolerància a la glucosa
- Infeccions oportunistes
- Síndrome gripal
- Aplàsia medul·lar
- Hepatotoxicitat
- Pancreatitis
- Risc de neoplàsia

En cas de patir algun efecte indesitjat vostè haurà de comunicar-ho al seu metge i l'investigador és qui decidirà quina és l'actitud més convenient a seguir.

La participació en aquest assaig clínic és totalment voluntària i el fet de signar el full del consentiment informat no l'exclou del dret de revocar el consentiment informat en el moment que ho consideri necessari.

El maneig de les dades serà totalment confidencial d'acord amb la "Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal" i les dades seran usades únicament per amb finalitat d'investigació clínica.

FULL DE CONSENTIMENT INFORMAT

Jo, _____, accepto participar en l'assaig clínic sobre l'ús de tacrolimus o azatioprina en el tractament de la miastènia gravis, i declaro que:

- He llegit amb atenció la fulla informativa de l'estudi on apareixen les seves finalitats i implicacions.
- He tingut l'oportunitat de preguntar els dubtes i aquests m'han sigut resolts satisfactòriament per part del personal de salut.
- La meva participació en l'estudi és voluntària.
- Les dades obtingudes seran usades únicament per a investigació clínica i seran tractades de forma confidencial.
- Comprenc que puc revocar el consentiment prèviament signat en qualsevol moment i sol·licitar l'eliminació de les dades aportades, sense haver de donar explicacions i sense que aquest fet alteri la meva assistència sanitària posterior.

Signatura del pacient Signatura del investigador

Lloc i data: _____, ____ de _____ del 20___

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____, revoco el consentiment prèviament signat per la participació en l'assaig clínic especificat a dalt.

Signatura del pacient Signatura del investigador

Lloc i data: _____, ____ de _____ del 20___

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