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## Myasthenia Gravis – Current Treatment Standards and Emerging Drugs

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### 1. Introduction

Myasthenia gravis is very rare disorder resulting from the autoimmune destruction of postsynaptic membrane in neuromuscular junction. In the most cases, antibodies bind to nicotinic acetylcholine receptors (nAChR), although other structures (e.g. muscle specific tyrosin kinase; MuSK) can be targeted as well. Binding antibody initiates immunological attack leading to reduced density of nAChR, simplification of the membrane and consequently to impaired neuromuscular transmission (Santa 1972). Clinical manifestation of the disease is described as fatiguable weakness of the striated muscles, which is painless and usually worsen after exercise. Initial symptom is asymmetrical ptosis of the upper eyelids frequently accompanied by the diplopia or blurred vision. An extension to another facial muscle groups can lead to expressionless appearance and difficulties with swallowing, chewing and speaking. The disease has a progressive character and it may become generalized after some time. The severe cases of MG require close monitoring of patient vital functions, because the risk of dyspnoea arises with the weakness of the intercostal muscles and diaphragm (Thanvi 2004).

Myasthenia gravis, formerly a lethal disease, may be now effectively treated, returning patient back to normal life. Nowadays, the treatment can be individualized to every patient according to the age and co-morbidities thanks to the wide variety of drugs available for different form and severity of the disease. Different approaches in the treatment strategy and possibility of combining them also allow minimization of the adverse effects.

## 2. Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors (AChEIs) were first introduced to the clinical practice by Mary B. Walker in 1930's. She studied the similarities in the symptoms of curare poisoning and Myasthenia gravis during administration of physostigmine (curare antidote). She observed a temporary improvement in the muscle weakness of MG patient (Walker 1934).

AChEIs still remain the first-line treatment in the initial stages or in the mild forms of the disease. They are also administered to the patients, who experience residual weakness, while using immunotherapy or those, who cannot receive immunosuppressive treatment (Juel 2007). AChEI slow down the degradation of acetylcholine (ACh) by acetylcholinesterase (AChE; Fig. 1). They increase ACh levels in the synaptic cleft and thus enhance impaired cholinergic transmission presuming that there is sufficient amount of the nicotinic acetylcholine receptors (AChR) left (Richman 2003). However, they provide only symptomatic treatment and do not modify the underlying progress of the disease.

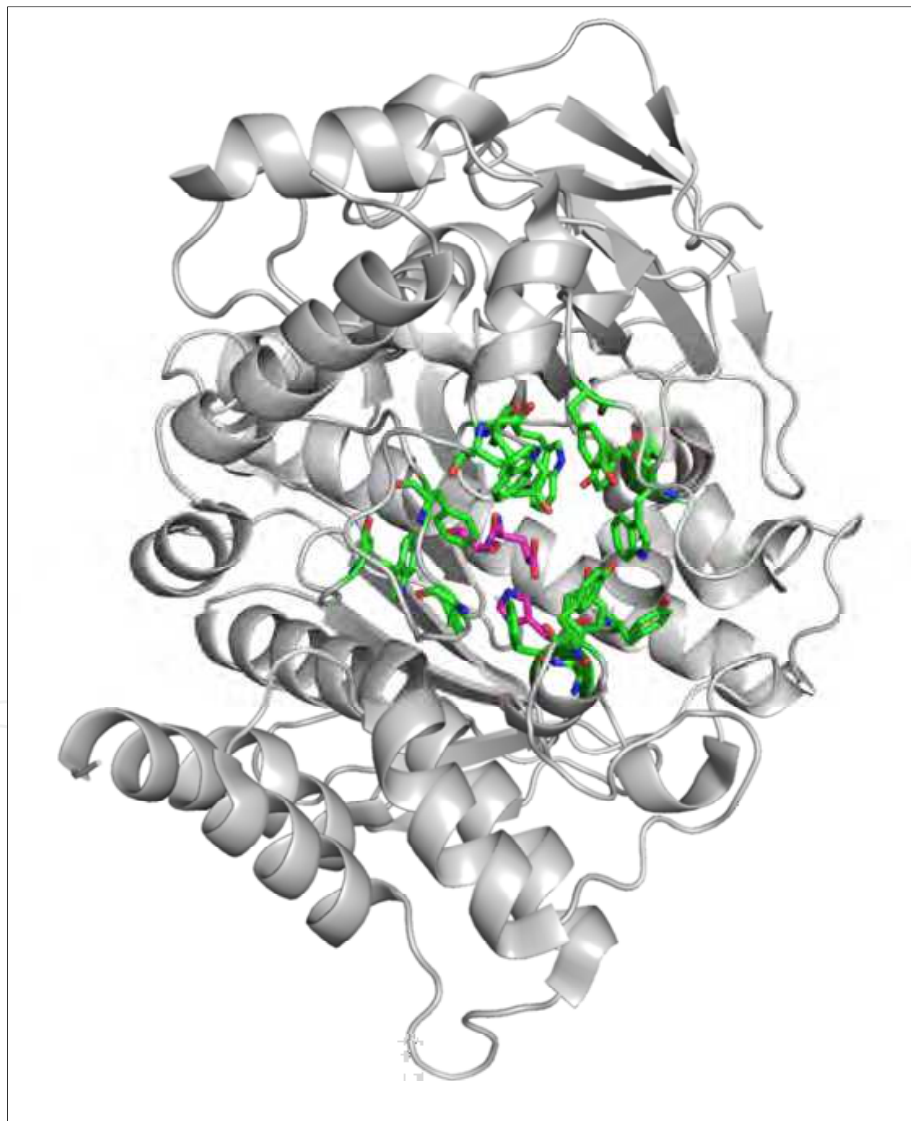


Fig. 1. Human recombinant acetylcholinesterase (1b41.pdb) with important aromatic residues (in green) and catalytic triade (in magenta).

Peripheral AChEI currently used in the therapy of MG are charged molecules usually containing one or two quaternary nitrogen in their structure. Most of them are derived from carbamic acids (pyridostigmine bromide, neostigmine bromide, distigmine dibromide). The non-carbamate bisquaternary drug ambenonium dichloride is structurally distinct representative of AChEI, and it has one of the highest affinities to AChE (Hodge 1992).

Effective dosing must be individualized to each patient according to his age, gender and eventual co-morbidities. Gastrointestinal side effects are related to the increased muscarinic activity produced by mentioned drugs and include nausea, vomiting, abdominal cramping and diarrhea. They can be treated with antimuscarinics (loperamide hydrochloride, diphenoxylate hydrochloride, propantheline bromide) without the loss of nicotinic effect (Hill 2003, Thanvi 2004). High doses of AChEI can lead to a cholinergic crisis characterized by even greater muscular weakness accompanied by increased bronchial secretion, diarrhea, abdominal pain, hypersalivation and bradycardia (Juel 2007; Thanvi 2004; Garcia-Carrasco 2007).

## 2.1 Pyridostigmine

Pyridostigmine (Mestinon®, Regonol®, Fig. 2; Urban 1951) Pyridostigmine bromide is the most globally used AChEI in the MG treatment. It is generally better tolerated than neostigmine bromide and has fewer gastrointestinal side effects (Juel 2005). The dosing often starts at 30 mg of pyridostigmine three times a day and can be increased up to 90 mg three or four times a day. The improvement in muscle strength usually develops 30 minutes after ingestion and lasts for four hours (Juel 2007).

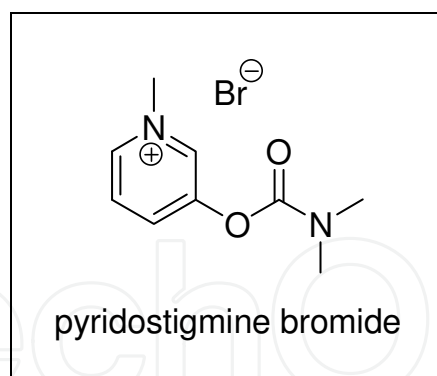


Fig. 2. Pyridostigmine bromide.

## 2.2 Neostigmine

Neostigmine (Prostigmine®, Vagostigmine®, Fig. 3; Aeschlimann 1933) has a rapid onset but its effect lasts only 2-3 hours. It is prescribed for patients with ocular MG. It is possible to administer neostigmine intravenously or subcutaneously, if the patient is experiencing difficulties with swallowing. More recently, a nasal application was successfully tested (Sghirlanzoni 1992).

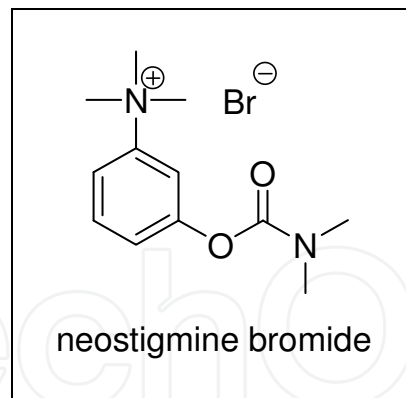


Fig. 3. Neostigmine bromide

### 2.3 Distigmine

Distigmine (Ubretid®, Fig. 4; Schmid 1957) is AChEI with prolonged effect (12-16 hours). It is used by patients without fluctuating physical exercise usually twice a day in the dose of 5 mg. Its prolonged effect is used for the patients experiencing the morning weakness, when it is administered in the evening the day before (Haward 1990).

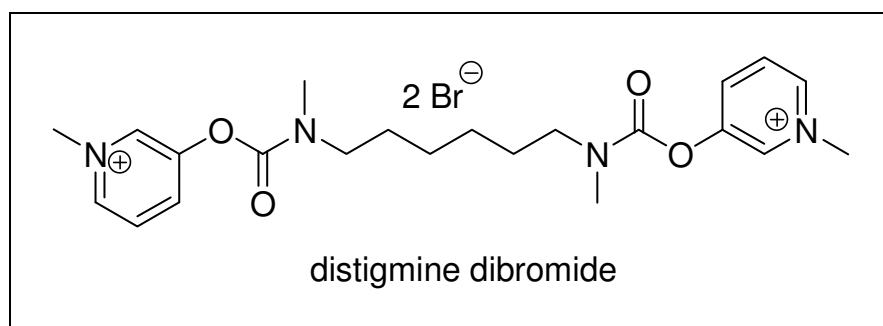


Fig. 4. Distigmine dibromide

### 2.4 Ambenonium

Ambenonium dichloride (Mytelase®, Fig. 5; Kirchner 1958) is AChEI with slower onset and prolonged pharmacological effect. It can improve clinical state of the patient, who has received other AChEI for a long time. The dosing is very individual and is usually 3-4 times a day up to 10 mg. Its side effects manifest very inconspicuously and cholinergic crises can be very dramatic (Verma 1992).

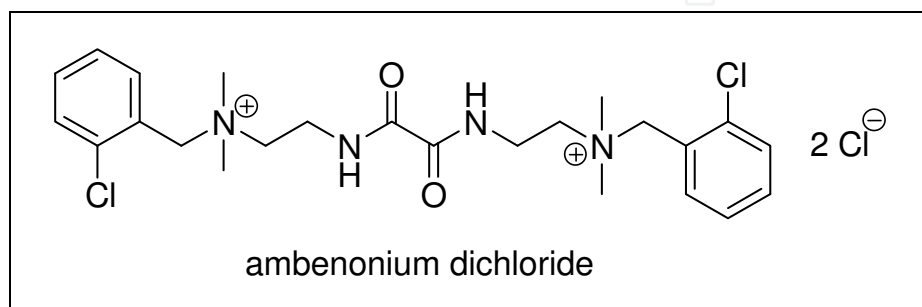


Fig. 5. Ambenonium dichloride.

## 2.5 Novel peripherally acting AChEIs

Despite the clinically used AChEI, there are many other peripherally acting AChEI with possible use for early MG stages (Komloova 2010). Many of such compounds were developed during the last decade. For this MG purposes, edrophonium like AChE inhibitors were prepared and they valuably showed sub-nanomolar AChE inhibition (Leonetti 2008). The bis-pyridinium heterodimers also proved high inhibitory potential (nanomolar range) and selectivity towards AChE compared to butyrylcholinesterase or choline kinase (Conejo-Garcia 2011). Similarly, the bis-pyridinium, bis-quinolonium and bis-isoquinolinium homodimers presented high AChE inhibition (nanomolar range) and some of them improved selectivity towards AChE (Musilek 2010, Musilek 2011, Komloova 2011). Such compounds might become the aim of further interest after essential *in vitro* and *in vivo* evaluation and they might lack the side effects of currently used AChEIs.

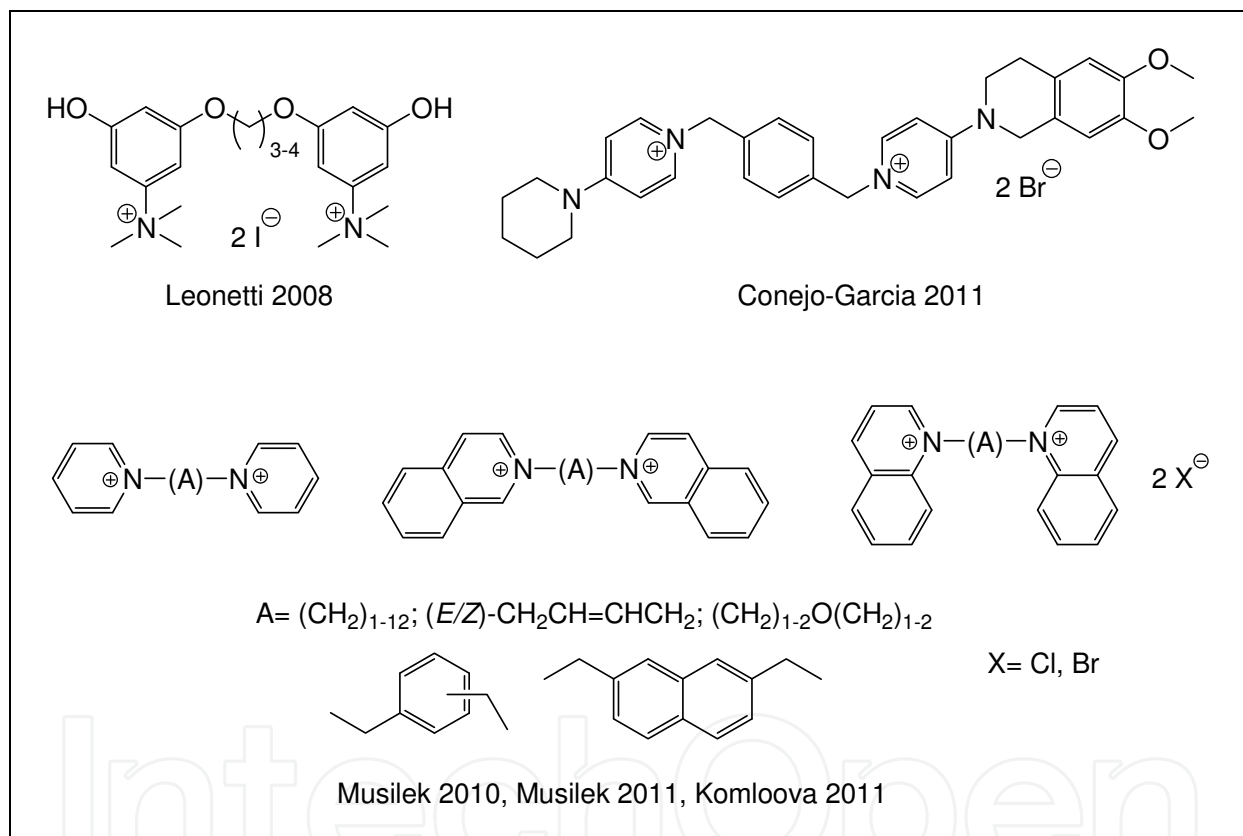


Fig. 6. Novel AChEIs tested for possible MG use.

## 3. Corticosteroids

Since a corticosteroid treatment is efficient in many autoimmune diseases, they are also used in the MG treatment, although their mechanism of action is not fully explained (Schneider-Gold 2005). Their interference with the immune system leads to anti-inflammatory, anti-allergic and anti-proliferative effect. Additionally, an increased expression and stabilization of acetylcholine receptors was observed in a long term administration of corticosteroids (Braun 1993). The corticosteroids belong to the standard treatment of MG moderate forms and MG mild forms insufficiently responding to the treatment with AChEIs.

The administration of corticosteroids is very often connected to the large amount of the adverse effects that are dose-dependent and may become very serious. For these reasons, it is important to minimize effective steroid dose individually for each patient. The side effects developed during corticosteroid treatment are metabolic disorders (hyperlipidemia, diabetes mellitus and potassium loss), hypertension, gastric ulceration, osteoporosis, cataracts, glaucoma, reduced immunity, muscle atrophy or psychic disorders (Juel 2007).

### 3.1 Prednisone

Prednisone (Decortin<sup>®</sup>, Encorton<sup>®</sup>, Fig. 6; Oliveto 1959) is the most used corticosteroid for MG treatment. There are two known approaches in its dosing strategy. The first approach starts with high daily dose of prednisone (from 1.5 -2.0 mg/kg/day or 60-80 mg/day), which is maintained for 2 -4 weeks and the dosing is modified to alternate day schedule (100-120 mg every other day) after the sufficient muscle improvement. The dose is then gradually decreased to minimize the side effects, while there is still satisfactory response in the muscle strength (Juel 2005). The reduction of the steroid dosage must be performed slowly and adequately to the responses of the patient, because the myasthenic relapse can occur and a rapid withdrawal of the steroid may result into myasthenic exacerbation and crisis (Juel 2007). Consequently, the dose reduction is performed in 4-8 week intervals from 10 mg to 30 mg/alternate day and then from 5 mg to 20 mg/alternate day (Juel 2005). Some patients do not tolerate this alternate-day schedule, because of the mood instability or difficult glycaemia control in the case of diabetic patients (Juel 2007). This alternate-day treatment may also require additional immunosuppressive treatment in the days without corticosteroids.

The second approach starts with 10-20 mg/day and increases the dose by 5-10 mg/week up to maximum dose of 50-60 mg/day until the satisfactory improvement in the muscle strength occurs. The dose is then gradually reduced to minimize the side effects (Schwendimann 2005, Seybold 1974, Sghirlanzoni 1984).

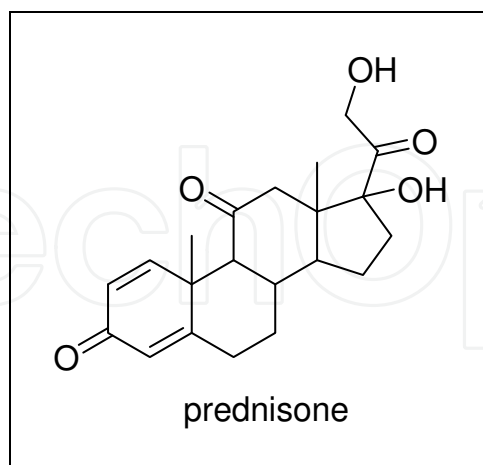


Fig. 6. Prednisone.

## 4. Immunosuppressants

Long-term corticosteroid treatment is usually connected with many serious dose-dependent side effects. Conventional immunosuppressants are used in MG to help to avoid these

corticosteroid side effects. They act more selectively on specific phases of the cell cycle. Azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil and tacrolimus are the most utilized immunosuppressants in the MG treatment. They can be combined together, or with glucocorticosteroids, allowing reduction of corticosteroid doses and thus minimizing the side effects. If used in monotherapy, it takes a certain time before the effect of these drugs is manifested. It is therefore recommended to start the immunosuppressive treatment along with corticosteroids and then gradually reduce the corticosteroid dosing.

#### 4.1 Azathioprine

Azathioprine (Imuran®, Azamun®, Fig.7) is the most often used steroid-sparing immunosuppressant (Hitchings 1962). It has few side effects and it is generally better tolerated in the long-term treatment compared to corticosteroids (Kokontis 2000). Azathioprine is an anti-metabolite. After ingestion, it is metabolized into 6-mercaptopurine, which is an inhibitor of purine synthesis and subsequently proliferation of rapid growing cells, especially lymphocytes (Juel 2007). The initial dose is 50 mg/day partially increased every week into optimal treatment dose of 2-2.5 mg/kg/day (Saperstein 2004, Schwendimann 2005). Application of azathioprine in combination with prednisone was found very advantageous thanks to slow onset of azathioprine effect. This combination also allowed the reduced dosing of both drugs (Gajdos 1983, Mantegazza 1988).

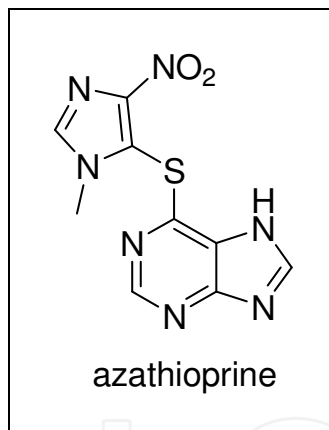


Fig. 7. Azathioprine.

Side effects of azathioprine consist in hepatotoxicity, myelo-suppression, potential carcinogenesis and teratogenesis, rarely alopecia and increased risk of lymphoma after long-term use (Herrlinger 2000). In 10-15% patients, an idiosyncratic allergy with rash, fever, nausea, vomiting and abdominal pain can occur (Hohlfeld 1988, Kissel 1986).

#### 4.2 Cyclophosphamide

Cyclophosphamide (Cyclophosphamid®, Fig. 8; Arnold 1958) is a cytostatic drug with the alkylating mechanism of action used primarily in the treatment of cancer (Zhu 1987). It is metabolized by hepatic oxidases into phosphoramidate mustard, active form of cyclophosphamide, responsible for its alkylating and cytotoxic properties. Cyclophosphamide is very toxic agent with teratogenic, carcinogenic and myelotoxic side



effects. It may also cause hemorrhagic cystitis and sterility (Richman 2003). It is reserved for patients with severe forms of MG and in combination with corticosteroids for those, who do not respond adequately to the treatment with corticosteroids alone (De Feo 2002). Common dosing is 100-200 mg daily.

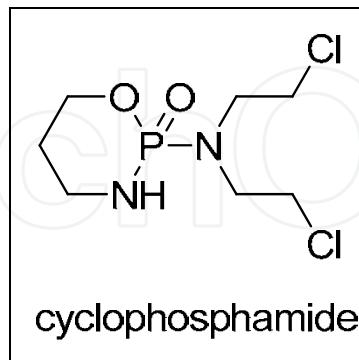


Fig. 8. Cyclophosphamide.

#### 4.3 Cyclosporine

Cyclosporine (Sandimmun®, Consupren®, Fig. 9) is a cyclic polypeptide produced by *Tolypocladium terricola* (Hassan 1987). His high nephrotoxicity and numerous interactions with other drugs make it a second choice immunosuppressant, reserved for patients with generalized severe MG form refractory to conventional treatment (Kahan 1989, Nyberg-Hnasen 1988).

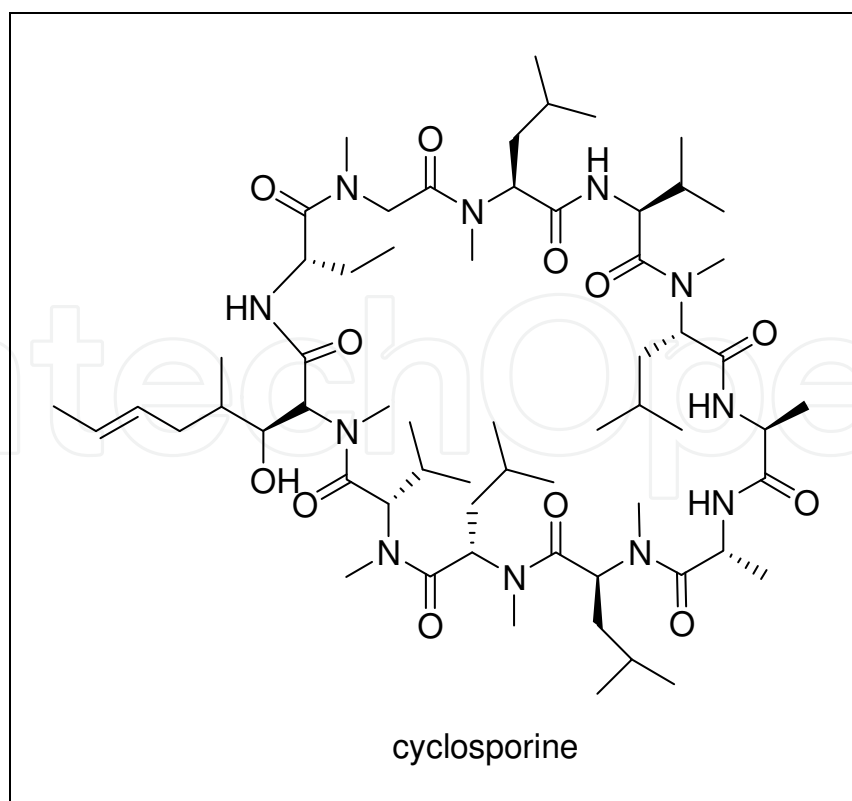


Fig. 9. Cyclosporine.

Cyclosporine affects T-lymphocytes and inhibits production of IL-2 and other cytokines (Matzuda 2000). A randomized double-blind placebo-controlled study showed significant MG improvement in muscle strength upon the usage of cyclosporine (Tindall 1993). Standard cyclosporine dosage is 2.5 mg/kg every 12 hours to achieve serum level of 100-150  $\mu\text{g/liter}$ . The monitoring of cyclosporine levels in serum is required to maintain the therapeutic concentration and prevent nephrotoxicity. Apart from nephrotoxicity, cyclosporine produces other side effects such as hypertension, tremor, hirsuteness, headaches, nausea and gingival hypertrophy (Juel 2005). Recent studies also suggest that cyclosporine may induce carcinogenesis by the direct cellular mechanism including production of transformed  $\beta$ -growth factor (TGF- $\beta$ ; Hojo 1999).

#### 4.4 Tacrolimus

Tacrolimus (Prograf<sup>®</sup>, Advagraf<sup>®</sup>, Fig.10) is a relatively new found macrolide immunosuppressant isolated from *Streptomyces tsukubaensis* (Okuhara 1986, Kino 1987). Likewise cyclosporine A, tacrolimus affects T-lymphocytes through calcium-calcieneurin pathway inhibiting production of inflammatory cytokines, e.g. IL-2, IL-3, IL-4, IL-5 and TNF- $\alpha$  (Kawaguchi 2007). Immunosuppressant abilities of Tacrolimus have already been used successfully in the prevention of rejection of transplanted organs (Vincenti 2001) and treatment of other autoimmune disorders, e.g. systemic lupus erythematosus (Duddridge 1997, Solsky 2002) and rheumatoid arthritis (Gremillion 1999).

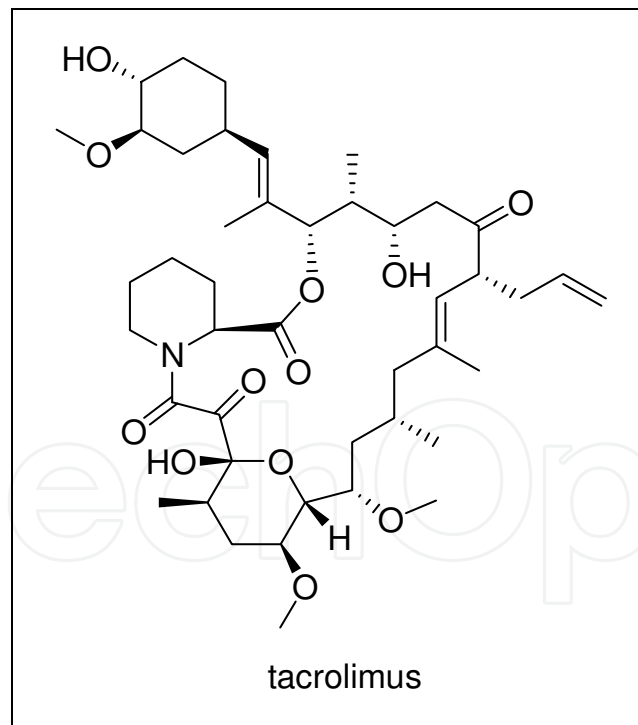


Fig. 10. Tacrolimus.

*In vitro* studies have also suggested that tacrolimus may enhance the effect of corticosteroids (Yang-Min 1993) allowing the reduction of doses in the steroid-dependent patients. Pharmacokinetic properties are highly individual for each patient and the dosage must be titrated in order to maximize the effect. It is usually administered orally in a dose of 3

mg/day and subsequently titrated to achieve blood levels of 10 ng/ml (Yang-Min 1993). Associated adverse effects are neurotoxicity, nephrotoxicity, impaired glucose metabolism (hyperglycemia through the reduction of insulin secretion; Nevins 2000), gastrointestinal discomforts and hypertension (Mayer 1997).

#### 4.5 Mycophenolate mofetil

Mycophenolate mofetil (CellCept®, Fig. 11) was originally designed to prevent rejection of transplanted organs, but additionally it became very useful in the treatment of many autoimmune diseases. It is a prodrug of mycophenolic acid (Alsberg 1912), antibiotic compound produced by *Penicillium brevi-compactum*, *P. stoloniferum* and related spp. Its mechanism of action consist in the blockade of purine nucleotides synthesis and consequently the inhibition of lymphocyte proliferation. It also helps to increased apoptosis of lymphocytes and monocytes (Cohn 1999) and reduces the secretion of immunoglobulines and inflammatory cytokines (Durez 1999, Eugui 1991). Its benefit in the MG treatment was demonstrated in many clinical trials (Chaudhry 2001, Ciafaloni 2001, Hauser 1998, Meriggioli 2003). However, its use is reserved for the patients with severe MG refractory to combination of corticosteroid/azathioprine treatment with standard dose of 1-1.5g twice a day (Juel 2005).

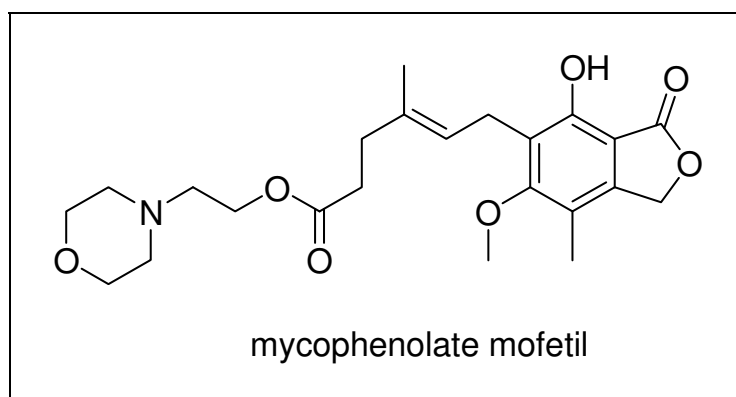


Fig. 11. Mycophenolate mofetil.

### 5. Biological treatment

The possibility of using products of immune system in the treatment of diseases was first mentioned by German scientist Paul Ehrlich in the beginning of 20<sup>th</sup> century. It took further 100 years, when an immunologic procedure could be involved in the practice. An important invention connected with progress in biological treatment was the discovery of preparation procedure for monoclonal antibodies by Caesar Milstein, Niels Kaj Jerne and George F. Köhler in 1975. Other representatives in the group of biological therapeutics apart from monoclonal antibodies are fusion proteins and the products of genome engineering designed to modify immunological response of the organism. These drugs are usually well tolerated and they offer advantageous alternative to conventional immuno-treatment (Sobotkova 2008).

### 5.1 Etanercept

Etanercept (Enbrel®, Fig. 12) is a fusion protein (Smith 1994, Jacobs 1997). These fusion or chimeric proteins are created by the connection of two genes coding originally two different proteins. Fusion protein combines properties of both original proteins. Etanercept is consisted from the human soluble receptor for tumor necrosis factor (TNF) linked to Fc portion of human immunoglobulin G<sub>1</sub>. Its dimeric structure increases its affinity to TNF- $\alpha$ . Its mechanism of action consists in the inhibition of the biological effect of TNF. Etanercept is administered subcutaneously 1-2 a week (Rovin 2008).

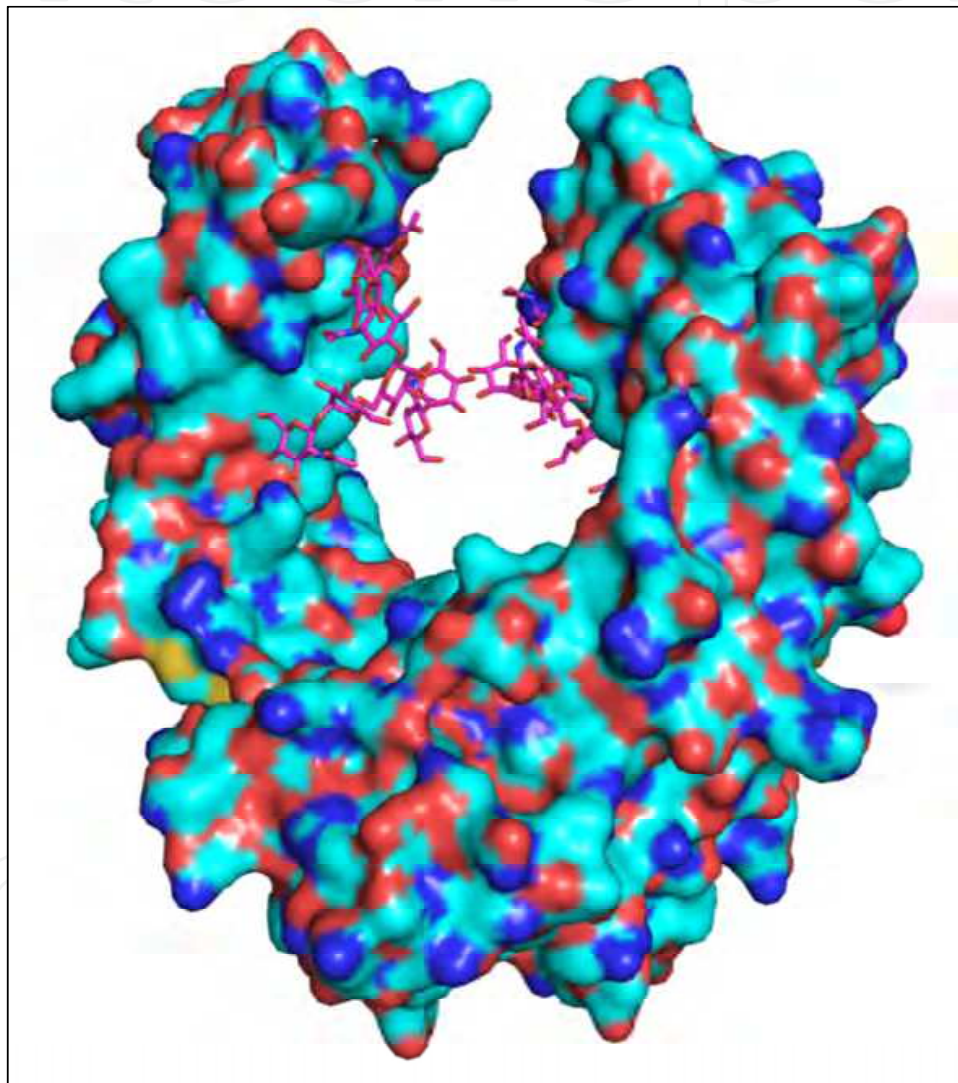


Fig. 12. Etanercept.

### 5.2 Rituximab

Rituximab (Rituxan®, MabThera®, Fig. 13) is a genetically engineered chimeric murine-human monoclonal antibody directed against the CD20 antigen found on B-lymphocyte

surface (Anderson 1994, Anderson 1998). The application of rituximab leads to depletion of B-lymphocytes, while other blood elements remain intact. After its use, the levels of serum immunoglobulins were minimally decreased. This finding led to assumption that the reduction of the immunoglobulin production is not the main mechanism of action in the treatment of autoimmune diseases. The drug is usually administered in the intravenous infusion. During the infusion, the rituximab rigor, fever and hypotension can develop as a result of released cytokines. More severe, but rare side effects are hypoxia and cardiovascular collapse (Yazici 2007; Eisenberg 2005).

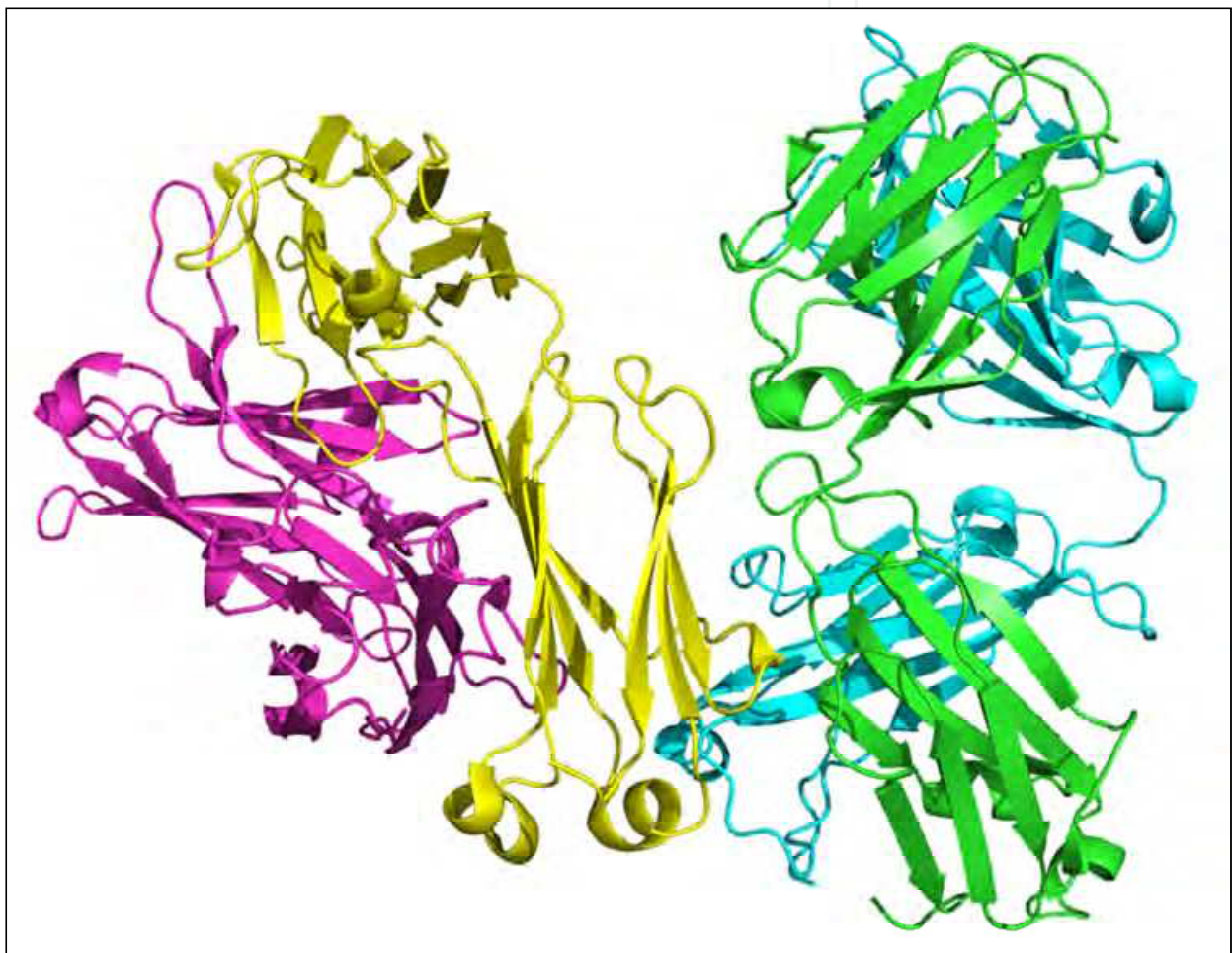


Fig. 13. Rituximab.

### 5.3 Basiliximab

Basiliximab (Simulect®, Fig. 14) is a human-murine chimeric monoclonal antibody directed against IL-2 receptor (CD25) antigen on the surface of T-lymphocytes (Amlot 1991). It is administered intravenously in a short infusion and its effect lasts for 4-6 weeks. There is the

enhanced risk of anaphylactic reaction during the application of basiliximab. Other side effects are headaches, anemia, hypertension, obstipation, diarrhea, nausea and infections (Pascual 2001; Kakoulidou 2008).

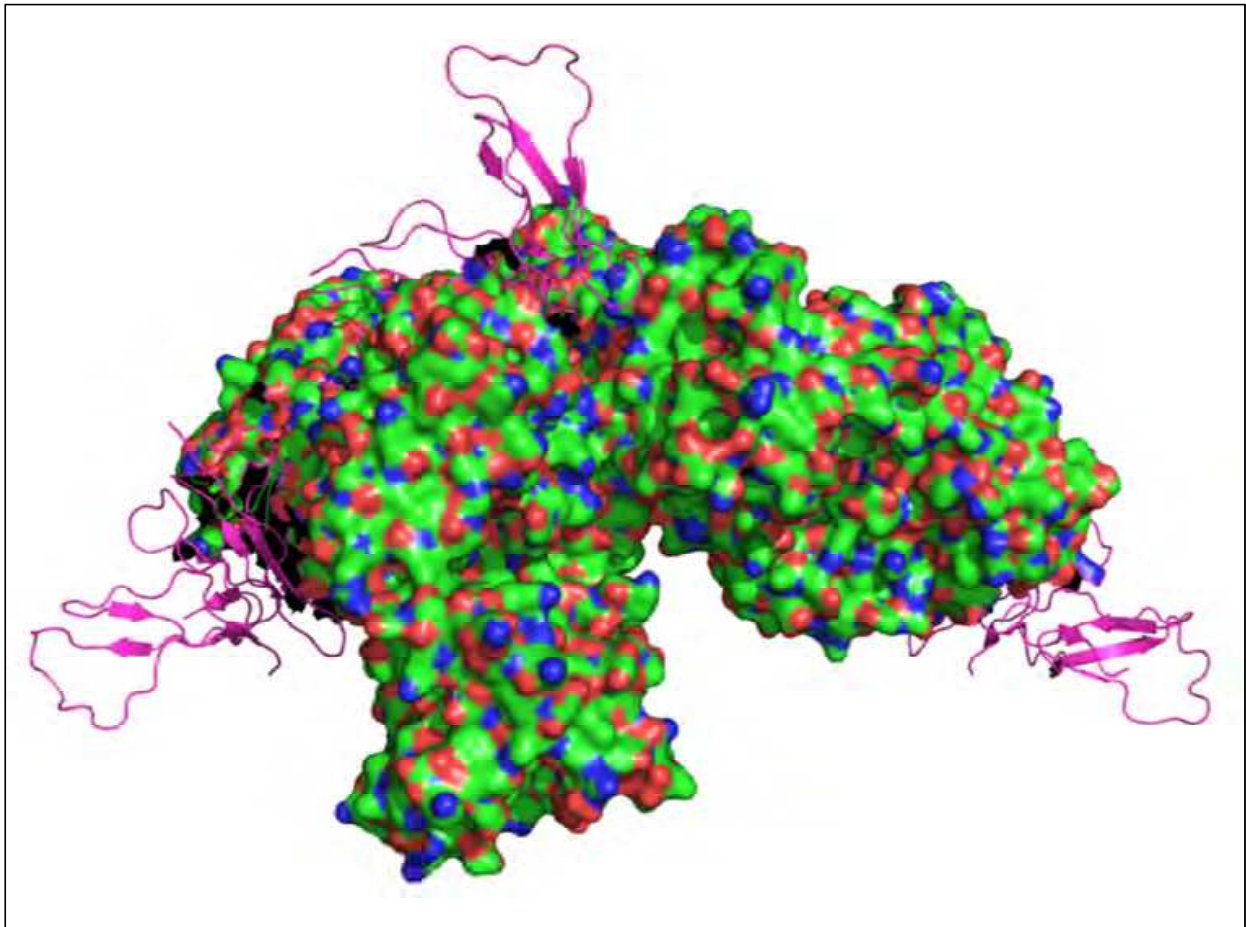


Fig. 14. Basiliximab.

#### 5.4 hEN101

A novel drug hEN101 (Monarsen®; Fig. 15) is now undergoing the clinical trials. It is a representative of so called “antisense therapy”, where an artificial strand of nucleic acid is designed and prepared to be complementary to mRNA, which transcript is known to be the cause of a disease (Soreq 2006). Binding of this artificial oligonucleotide to mRNA then forms an mRNA-antisense complex, which is destroyed by RNAses and the protein coded by mRNA is consequently not synthesized (Sussman 2008).

In the case of MG, the mRNA of AChE is the targeted structure. In the study performed by Brenner et al. on rats with experimental MG, the overexpression of so called “readthrough” transcript of AChE (AChE-R) was observed (Brenner 2003). AChE-R isoform might be

responsible for the increased degradation of ACh in the experimental MG in rats. This isoform of AChE differs from principal synaptic isoform (AChE-S) in the structure of the C-terminal sequence (Grisaru 1999) and unlike AChE-S it forms soluble monomer, which is not anchored in the postsynaptic membrane (Seidman 1995). These structural differences make AChE-R also more sensitive to hEN101 treatment even though it binds to coding sequence of common to all isoforms. hEN101 is a 20-mer oligonucleotide active both orally and intravenously (Brenner 2003).

5'-CTGCCACGTTCTCCTGCACC-3'

hEN101

Fig. 15. hEN101.

## 6. Conclusion

The current treatment options, variety of drugs with different mechanisms of action and their availability, as well as the individual approach to the each patient have improved greatly the prognosis of MG. Though the well known AChEI are offering only symptomatic treatment that is not affecting the original cause of the disease, they are valuable tools for early and mild MG forms. The corticosteroid treatment may be also successfully applied in mild MG stages, especially in combination with immunosuppressants that allow the reduction of corticosteroid dosage. However, the biggest disadvantage of AChEI, corticosteroids or immunosuppressants and even their combination consist in their very serious side effects. For these reason, the upcoming (emerging) biological treatment seems to be solution for MG treatment. The use of monoclonal antibodies and fusion proteins that possess the specific targeted effect and only few side effects is the great benefit for the patients and this benefit is also compensating the high costs of this treatment. Moreover, the antisense therapy might solve some more issues connected to MG treatment.

## 7. Acknowledgements

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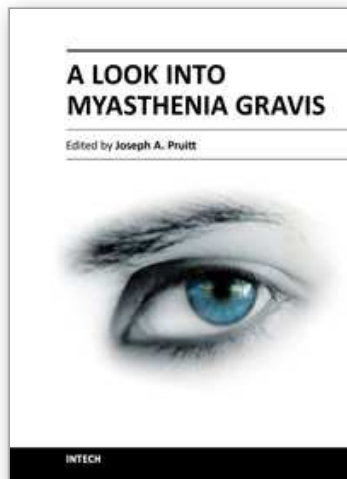
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Myasthenia gravis is presently an incurable antibody-mediated autoimmune disorder characterized by generalized voluntary skeletal muscle weakness. The cause of the weakness is a defect at the neuromuscular junction level, in which autoimmune antibodies block the receptors responsible for initiating muscular contraction. Literally translated from its Latin and Greek etymological roots, myasthenia gravis means "grave muscle weakness". Fortunately, advances in modern medicine have resulted in a reduction of the truly "grave" outcomes for those inflicted but, without a cure, the gravity surrounding the disease remains

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