

COMPOSITION COMPRISING ALBUMIN FOR USE IN THE TREATMENT OF AMYOTROPHIC
LATERAL SCLEROSIS (ALS) BY PLASMA EXCHANGE

DESCRIPTION

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The present invention relates to a composition comprising albumin for use in the treatment of amyotrophic lateral sclerosis (ALS) by plasma exchange.

10 Amyotrophic lateral sclerosis (ALS) is a motor neurone disease affecting about 3 of 100.000 people a year in United States. ALS is a chronic, progressive and fatal degenerative neurological disease that causes the death of motor neurons controlling voluntary muscles. For 90 % of cases, the origin of the disease is unknown and sporadic. Despite extensive studies on this disease, its pathogenesis has not been identified yet and no effective treatment has been found.

15 As previously mentioned, ALS is usually progressive, with upper and lower motor paralysis leading to an average survival of three years from the start of the disease. In general, difficult and distressing medical problems arise during the course of the disease, which have motivated the use of a wide variety of treatments, such as toxic drugs, inactivated cobra venom and plasmapheresis, among others.

20 Plasmapheresis is a common medical procedure in which plasma from a patient is separated from whole blood. It has been used to treat patients suffering from different chronic diseases. Once the plasma is separated from the blood cells, the cells can be returned to the patient with or without replacement fluids. During treatment of patients by therapeutic plasmapheresis, a catheter is placed in a major vein, for example in the arm, and a second catheter is placed in another vein, for example, in the foot or hand.

25 The blood then leaves the patient's body through the catheter and is sent to a separating device, where the plasma is separated from the blood cells. Blood without plasma and, optionally, along with replacement fluid, is returned to the patient through the second catheter. Instead of two peripheral catheters, a dual-channel, central, or peripheral catheter can also be used.

30 The use of plasmapheresis for the treatment of ALS has been previously reported. For example, Silani et al. used plasma exchange with frozen plasma and saline for the treatment of four ALS patients during six months (Silani, V., Scarlato, G., Valli, G. and Marconi, M. "Plasma Exchange Ineffective in Amyotrophic Lateral Sclerosis" Arch. Neurol. (1980) Vol. 37: 511-513). However said treatment was unsuccessful and did not change the course of the disease. In addition, in a later work of Kelemen et al., the use of plasma exchange with albumin at 5 % in combination with immunosuppressants for the treatment of ALS shown
35 no beneficial effect on the disease, nor any clinical improvement in any of the 4 patients studied (Kelemen, J., Hedlund, W., Orlin, J.B., Berkman, E.M. and Munsat T.L. "Plasmapheresis with immunosuppression in Amyotrophic Lateral Sclerosis". Arch. Neurol. (1983), Vol. 40: 752-753.).

40 These previous works explain why the use of plasma exchange in the treatment of ALS is considered of category IV (the lower) in the guidelines on the use of therapeutic apheresis in clinical practice by the American Society for Apheresis (Schwartz, J., Winters, J.L., Padmanabhan, A., Balogun, R.A., Delaney, M., Linenberger, M.L., Szczepiorkowski, Z.M., Williams, M.E., Wu, Y., Shaz B.H. "Guidelines on the use

of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue" J. Clin. Apher. 2013 Jul; 28(3):145-284). Category IV relates to disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful.

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More recently, it was shown in the Spanish Patent ES201530074 that the use of a composition comprising albumin for the treatment of ALS by plasma exchange could provide some beneficial effects on the course of the disease. In said Spanish Patent, an ALS patient was treated during 14 weeks with a composition comprising human albumin at 5 % (w/v) by plasma exchange 3 times a week during the 2
10 first weeks and once a week during the other 12 weeks. The effect of said specific treatment was evaluated using a functional qualification of ALS from a period starting 12 months prior the treatment and finalizing 2 months after the end of the treatment. The results of said functional qualification showed a tendency to stabilization of the course of the disease over time, which was unexpected since it is well known that a ALS patient's condition always tends to worsen.

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However, said study was conducted with only one patient for whom the course of the disease was maintained, but not improved in any way.

Therefore, there remains a need for a treatment of ALS by plasma exchange that could avoid the normal
20 progression of the disease and could even improve the functional qualification of the patient.

The inventors of the present invention have surprisingly found that the use of a composition comprising albumin for the treatment of ALS by plasma exchange could indeed improve the progression of the disease by using specific treatment conditions.

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Therefore, in a first aspect the present invention relates to a composition comprising albumin for use in the treatment of ALS by plasma exchange.

Preferably, the albumin concentration in said composition is between 5 % and 25 % (w/v). More
30 preferably, the concentration of albumin is about 5 %, 10 %, 15 %, 20 % or 25 % (w/v). Even more preferably, the concentration of albumin is about 5 % (w/v).

Albumin can be either recombinant or purified from human plasma. In a preferred embodiment, the albumin is purified from human plasma.

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In preferred embodiments of the present invention, the composition comprising albumin for use in the treatment of ALS is administrated to a patient in need thereof by plasma exchange using a volume of said composition equivalent to approximately 100 % of the volume of plasma withdrawn from the patient. In preferred embodiments, said composition is administrated to the patient by plasma exchange twice a
40 week the first 3 weeks and once a week for the following 21 weeks, for a total period of 24 weeks.

In the present invention, treatment with the composition comprising albumin is preferably carried out by plasma exchange, i.e. said composition comprising albumin is used as replacement liquid and will be

returned to the patient along with the blood cells, which have been previously separated from the plasma by plasmapheresis. In general, a determined volume of plasma is withdrawn from the patient and the plasma exchange with the composition comprising albumin is carried out with a volume of said composition equivalent to approximately 100 % of the volume of plasma withdrawn from the patient. A
5 person skilled in the art understands that small variations of approximately ± 10 % of this volume will fall within the scope of the present invention.

One of the main difference from the use of a composition comprising albumin for the treatment of ALS according to the present invention and the treatments known in the prior art, is that in the present
10 treatment the use of immunosuppressants is not necessary before, during or after finishing said treatment. ALS has been linked in the prior art to abnormalities of the immune system such as abnormalities of surface antigens, T lymphocytes, and macrophage migration (Kelemen J. et al., Above), which may suggest the use of a concomitantly immunosuppressant treatment with any ALS treatment. However, it is demonstrated herein that the use of immunosuppressants is not necessary with the
15 treatment of the present invention to obtain satisfactory results for the treatment of ALS. Thus, in some embodiments, the use of immunosuppressants is not required during the treatment with the composition of the present invention. However, in other embodiments, the use immunosuppressants during the treatment of ALS with the composition of the present invention is also possible if required by other conditions of the patient.

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In the treatment of the present invention, the plasma exchange using the composition comprising albumin as replacement fluid is carried out with a frequency of twice a week the first 3 weeks and once a week during the following 21 weeks, which correspond to a total period of 24 weeks.

25 During the duration of the treatment according to the present invention, patients may experience, at least, a tendency to stabilize the course of the disease. In other words, since ALS is a disease whose progression is rapid and gradual once ALS symptoms onset, achieving stabilization of its progression during the duration of the treatment can be considered a very positive result. In addition to that, the treatment of the present invention has also demonstrated to improve the functional qualification of some
30 of the patients and therefore, to reverse the progression of the disease to less advanced stages.

In a second aspect, the present invention relates to a method for treating ALS in a patient in need thereof, comprising the administration of a composition comprising albumin by plasma exchange. Preferably, said plasma exchange is carried out using a volume of said composition equivalent to
35 approximately 100 % of the volume of plasma extracted from the patient. A person skilled in the art understands that small variations of approximately ± 10 % of this volume will fall within the scope of the present invention. In some preferred embodiments, said method for treating ALS is carried out with a frequency of twice a week the first 3 weeks and once a week during the following 21 weeks, for a total period of 24 weeks.

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Preferably, the albumin concentration in said composition is between 5 % and 25 % (w/v). More preferably, the concentration of albumin is about 5 %, 10 %, 15 %, 20 % or 25 % (w/v). Even more preferably, the concentration of albumin is about 5 % (w/v).

Albumin can be either recombinant or purified from human plasma. In a preferred embodiment, the albumin is purified from human plasma.

- 5 In some embodiments, the use of immunosuppressants is not required during the method for treating ALS of the present invention.

Hereinafter, the present invention is described in more detail with reference to illustrative examples, which does not constitute a limitation of the present invention.

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EXAMPLE

Plasma exchange (PE) with albumin 5 % (Albutein®, Grifols, S.A., Spain) in patients diagnosed with ALS.

- 15 Men and women aged 18 to <70 years with a definite, possible or probable diagnosis of ALS according to El Escorial/Airlie House criteria, and having a forced vital capacity (FVC) >70 % of predicted value were eligible for a prospective, single-arm, single-center, pilot study.

- Patients underwent 6-month of PE-treatment using 5 % albumin (Albutein® 5 %) in 2 phases: one
20 intensive phase involving 2 PE sessions per week for 3 weeks, followed by a maintenance phase involving one PE session per week for 21 weeks. The follow-up period was 6-month.

- Endpoints were changes in Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score and FVC. Based on the typical survival of 3-5 years from time of ALS symptoms onset, and the
25 typical decrease of 1 point/month in the ALSFRS-R overall score, three categories of disease progression were defined: "normal", "slow", and "fast", depending on whether ALSFRS-R slope was between -0.8 and -1.33 points/month, < -0.8 points/month, or > -1.33 points/month, respectively.

- Thirteen adults with ALS were enrolled and evaluated. Median (IQR) overall score at baseline was 42.0
30 (37.0, 44.0). ALSFRS-R score declined throughout the study, although the median decline was less than expected in untreated patients. Seven patients at the end of treatment and 5 patients at the end of study had a slower decline than expected. Six patients remained in the same "progressor" category while 4 improved their category at the end of the treatment. Median (IQR) of FVC and predicted FVC percentage at baseline were 3.9 (3.0, 4.9) L and 87.0 % (76.0, 96.0), respectively. Median FVC decreased
35 significantly during the study. The treatment was well tolerated.

- Plasma Exchange with albumin replacement was safe and well tolerated in ALS patients. Although functional impairment progressed, most patients showed a slower than expected rate of decline at the end of treatment. In terms of slope progression most patients either remained stable (54.5 %) or
40 improved (36.4 %) their category.

Thus, the treatment of the present invention has been proved not only to stabilize the course of the disease but also to improve the conditions of the patients and therefore, to reverse the progression of the

disease to less advanced stages.

Although the invention has been described with respect to a preferred embodiment, this should not be considered as limiting the invention, which will be defined by the broadest interpretation of the following claims.