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Review Article

Possible treatments for sporadic Creutzfeldt-Jakob disease: a systematic review

Possíveis tratamentos para a doença de Creutzfeldt-Jakob esporádica: uma revisão sistemática

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ABSTRACT: Prion Diseases are rare and fatal diseases that compromises the Nervous System, in which occurs an abnormal accumulation of a protein known as Prion Scrapie (PrPsc). PrPsc is a mutation of a brain tissue protein called Normal Cellular Prion (PrPc) and the accumulation of PrPsc causes spongiform deficiencies. Creutzfeldt-Jakob Disease (CJD) is one of the various Prion Diseases and its sporadic form (sCJD) is the most prevalent. Considering the relentless and rapid progression of the disease, the invariably lethal outcome and the scarcity of therapeutic options for Prion Diseases, especially sCJD, effective treatments become necessary. Thus, the objective of this systematic review is to analyze and identify therapeutic options aimed at sCJD. This research was carried out in the *Pubmed* and *Cochrane* databases with the *Mesh Terms* "Sporadic Creutzfeldt-Jakob disease" and "Treatment", and the boolean "AND". Four articles in English were selected, that most aligned ones with the work targets. As the outcome of this research, came to a conclusion that two drugs were well tolerated by the patients, nevertheless they did not deliver a better life quality neither achieved an extended life span. Other drugs are being tested in adult patients, some in clinical trials exhibited good efficacy, minimizing cognitive deficits in CJD patients. However, the studies require a greater number of trials in a wide amount of patients for better conclusion that addresses the treatment of this severe and fatal disease.

Keywords: Prion disease; Sporadic Creutzfeldt-Jakob disease; Treatment.

RESUMO: As Doenças Priônicas são doenças raras e fatais que comprometem o Sistema Nervoso, na qual ocorre um acúmulo anormal de uma proteína conhecida como Prion Scrapie (PrPsc). A PrPsc é uma mutação de uma proteína do tecido cerebral chamada Prion Celular Normal (PrPc) e o acúmulo de PrPsc causa deficiências espongiformes. A Doença de Creutzfeldt-Jakob (CJD) é uma das várias Doenças Priônicas e sua forma esporádica (CJDe) é a mais prevalente. Considerando a progressão implacável e rápida da doença, o desfecho invariavelmente letal e a escassez de opções terapêuticas para as Doenças Priônicas, especialmente a DCJ, tratamentos eficazes tornam-se necessários. Assim, o objetivo desta revisão sistemática é analisar e identificar opções terapêuticas voltadas para a DCJe. Esta pesquisa foi realizada nas bases de dados Pubmed e Cochrane com os termos Mesh "Sporadic Creutzfeldt-Jakob disease" e "Treatment", e o booleano "AND". Foram selecionados quatro artigos em inglês, que mais se alinhavam com os objetivos do trabalho. Como resultado desta pesquisa, chegou-se à conclusão de que dois medicamentos foram bem tolerados pelos pacientes, porém não proporcionaram uma melhor qualidade de vida e nem alcançaram maior longevidade. Outros medicamentos estão sendo testados em pacientes adultos, alguns em ensaios clínicos apresentaram boa eficácia, minimizando déficits cognitivos em pacientes com DCJ. No entanto, os estudos necessitam de um maior número de ensaios em uma grande quantidade de pacientes para melhor conclusão que aborde o tratamento desta doença grave e fatal.

Palavras-chave: Doença priônica; Doença de Creutzfeldt-Jakob esporádica; Tratamento.

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INTRODUCTION

Prion diseases, or Transmissible Spongiform Encephalopathies (TSEs), are rare and degeneratve diseases that compromises the Nervous System, in an irreversible process, in which occures of an abnormal accumulation of a protein, called Prion Scrapie (PrPsc), well known only as Prion[1]. PrPsc is an infectious pathogen devoid of nucleic acid and is characterized by the modified form of a protein existing in brain tissue, located in the cell plasma membrane, especially in neurons associated with synapses, called Normal Cell Prion (PrPc). The role of PrPc is still unknown. Possible physiological roles are the action of ferrireductase and modulation of iron transport in the cornea, neuroprotection, resistance to virus infection in various tissues, synaptic plasticity in the hippocampus, copper binding and cell adhesion[2].

The infectious form presents structural differences when compared to the normal form, which influence its physicochemical properties, such as solubility, fibril formation and resistance to cleavage mediated by K proteins. The most striking structural difference between the cellular and pathological forms is related to the configuration of their protein structures, in which PrPc has 5% of pleated β-sheets, while PrPsc represents 43% of the total[1,2,3].

The disease occurs from a mutation in the Prnp gene that encodes the normal form (PrPc), modifying this protein to its altered form (PrPsc). The modified form multiplies by inducing its normal counterpart to assume the pathogenic configuration, initiating a domino effect, in which more and more brain proteins are converted into the form that causes the disease, which favors protein aggregation and fiber formation. Vacuolized neurons, gliosis and neuronal loss are also observed, which lead to apoptosis and cell death in the nervous tissue, forming lesions with a spongiform texture that progressively result in death[1,2,3,4].

Creutzfeldt-Jakob disease (CJD) is the most common form of human prion disease, responsible for most cases of the disease, with progressive evolution and, in most cases, fatal, after 4 months to 2 years of infection. The disease mainly affects individuals over 40 years of age. There are three types of presentation of CJD: the familial form, where the disease is transmitted genetically, the acquired form, especially through contact with food and substances contaminated with PrPsc, and the sporadic form of uncertain and sudden origin. It is noteworthy that all forms of CJD are transmissible, regardless of their etiology. The sporadic CJD (sCJD) does not arise from contamination, in contrast to the acquired form, being responsible for most cases of the disease (about 85% of all cases). sCJD originates from a self-mutation in the format of normal PrP proteins[1,4].

Considering the rapid progression of the disease, the invariably lethal outcome and the scarcity of therapeutic options for Prion diseases, especially sCJD, the study of possible therapies aimed at curing or increasing patient survival is necessary.

OBJECTIVE

Analyze and identify possible targeted therapeutic options for sporadic CJD according to clinical trials.

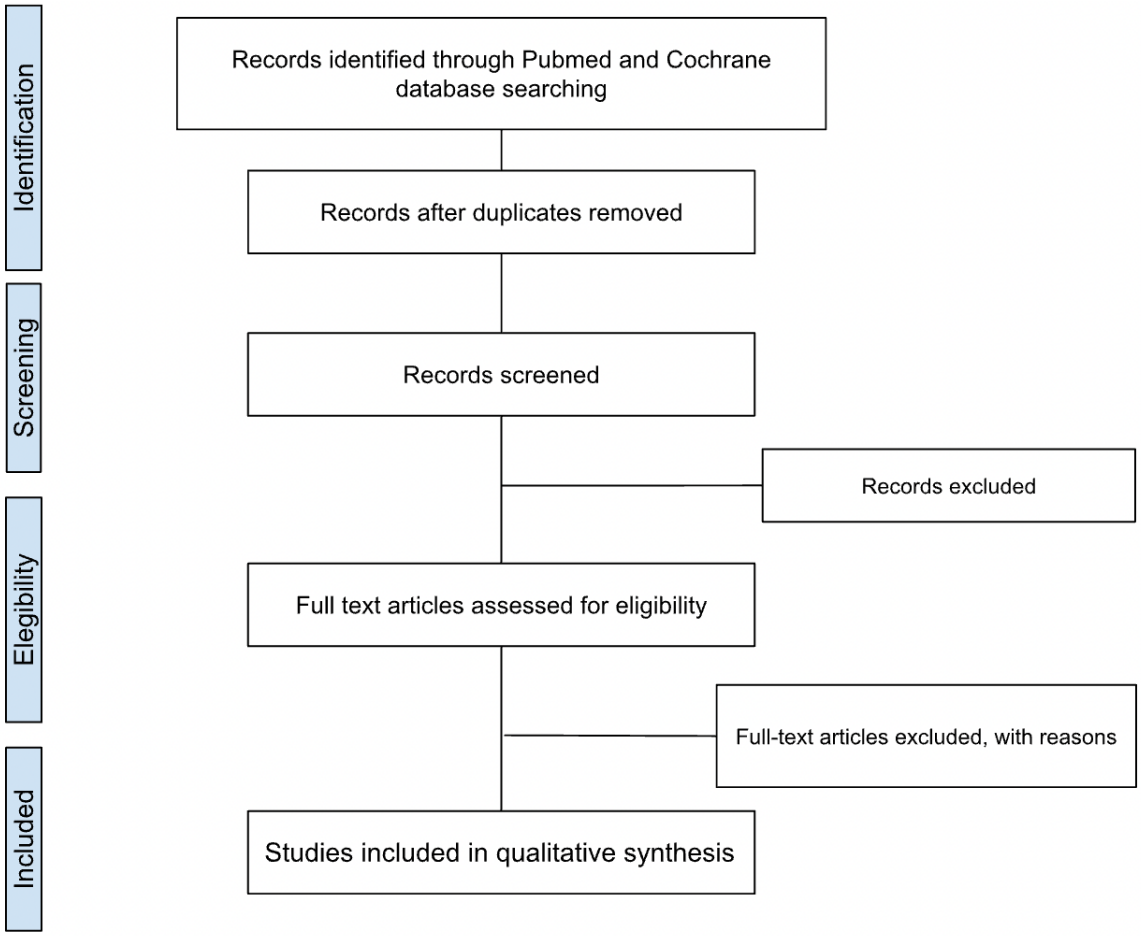
METHODOLOGY

For the development of this systematic review, the research question was elaborated using the PICO strategy, in April 2022. The study population consisted of patients who had previously been diagnosed with Creutzfeldt-Jakob disease, in order to know what would be the best therapies to manage this condition. As a search strategy, it was carried out in *PubMed* and *Cochrane* databases with the *MeSH (Medical Subject Headings) terms* "Prion disease", "Sporadic Creutzfeldt-Jakob Disease" and "Treatment" and the boolean "AND". The research was based only on clinical trials and randomized clinical trials, in Portuguese and English, from the last 15 years, as there are few studies related to therapeutic treatments for Creutzfeldt-Jakob disease in recent years.

The search and selection of articles were carried out by the main author and co-authors and, for the proper systematization of the data and its reproducibility, the PRISMA® platform was used, following the proposed guidelines. The review was registered on the PROSPERO® platform[5]. For greater adequacy to the theme, the exclusion criteria formulated were articles that, after a thorough reading, do not fit the theme of the present study, being it referring to clinical trials related to therapeutic options for sCJD. The selection of articles was made exclusively by the analysis of the methodology used, not considering the journal or author of the clinical trials.

To assess the effectiveness of interventions and avoid major sources of bias among participants for treatment or control, Randomized Clinical Trials (RCTs) were chosen to compose this review. However, the study by Collinge et al.[5] is considered, in principle, an observational study, in which patients have the right to choose the study sequence (Patient Preference Trial method), with 2 patients choosing randomization, and therefore the study was selected.

The summary of the article selection methodology, reproduced according to the PRISMA platform, is shown in Figure 1.



Adapted from Liberati, et al. (2009)[5].

Figure 1 - Flowchart used to obtain the articles included in the review using the PRISMA® protocol

RESULTS

A total of 4 studies were identified to include the review. The search in *Pubmed* and *Cochrane* databases resulted in 360 citations. After deleting the duplicates, 357 articles remained. With the application of the search filters, 347 were discarded. After reading the title and abstract of the 10 articles found, 4 studies were included in the systematic review.

Studies were analyzed based on their methodology and study design, as well as patient follow-up. The level of evidence for each study is presented in the last column of Table 1.

Table 1- Reliability table

Trials	RCT	RCT Stopped Early	Patients Blinded	Health Care Providers Blinded	Patients Discontinued Study	Level of Evidence**	Grade of Recommendation
Collinge et al.*	Yes	Yes	n=0	No	n=2	Level 2B	B
Geschwind et al.	Yes	No	n=54	Yes	n=29	Level 2B	B
Haïk et al.	Yes	Yes	n=121	Yes	n=4	Level 1B	A
Varges et al.	Yes	No	n=12	Yes	n=7	Level 1C	B

Note: RCT, randomized controlled trial.
* Patient preference trial, the study has one arm of randomization, with no placebo use.
** Classification according to Levels of Evidence for Therapeutics Studies of the Center for Evidence Based Medicine (CEBM)[6].
--- No aplicable
Adapted from Liberati A et al., 2009.

The data for each study are simplified in Table 2 and Table 3. In Table 2, some characteristics of each trial are found, such as author's name and year of publication, drug administered and medication dosage, study design and findings, and number of patients alive at the end of the study. In Table 3, some data such as the study population and its characteristics, and study time, are compiled.

Table 2 - Characterization of the studies included in the research.

Author/year	Objective	Medication	Study design	Findings	Number of subjects alive at the end of the study
Collinge et al. 2009	Obtain data on the effect of Quinacrine on prion disease	Oral Quinacrine 200mg/6 hours and 100mg 3 times/day	Patient preference trial	No difference between the survival rates	26
Geschwind et al. 2013	To determine whether oral Quinacrine 300 mg daily for 2 months increases survival in CJD	Oral Quinacrine /200mg every 6 hours, followed by 100mg three times a day	DB RCT	Didn´t show any improvement on the survival rate	32 at month 2
Haik et al. 2014	To assess the effectiveness of Doxycycline in increasing survival rate the safety of the treatment and its effects on the rate of disease progression	Oral Doxycycline 100mg daily	DB RCT	Didn´t show any improvement on the survival rate	17
Varges et al. 2016	Study the therapeutic efficiency of Doxycycline on subjects with sCJD	Oral Doxycycline 100mg daily	DB RCT	Was observed an increase in the survival rate of subjects with Doxycycline	0

DB, Double Blind; RCT, Randomized Controlled Trial.
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Tablet 3 - Characterization of the studies included in the research.

Author/year	Study Population			Characteristics of the study population		Study time
	Total	Received the medicine	Did not received the medicine	Sex	Average age	
Collinge et al. 2009	106	40	66*	n=50 M (47%) n=56 F (53%)	56 years	~16 months
Geschwind et al. 2013	51	23	28	n=31 M (60%) n= F (40%)	62 years	~4 years. The study gathering proceed for 1 year and 9 months after the study ended
Haik et al. 2014	121	62	59	n=51 M (42%) n=70 F (58%)	63 years	~3 years. However, the study had other time periods in both countries Italy: 2007 a 2010 / France: 2009 a 2012)
Varges et al. 2016	12	7	5	n=7 M n=5 F	64 years	2 years and 6 months

~, Approximately.
*Patient preference trial study, the patients chose to not receive medications. The other studies included placebo.
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DISCUSSION

Prion diseases are a group of rare neurodegenerative diseases caused by the continuous conversion of the PrPc protein into PrPsc. This structural change favors the aggregation of the altered protein and, later, the formation of amyloid fibers, which trigger the cell death of the nervous tissue. Consequently, there is the formation of lesions with a spongiform texture, which is why these diseases are known[1,7].

The TSE group includes some diseases, such as Scrapie, Kuru, Gerstmann-Straussler-Scheinker syndrome (SSG), Creutzfeldt-Jakob disease (CJD) and Fatal Familial Insomnia. CJD is the encephalopathy that most affects humans, being characterized as a fatal, degenerative neurological disease with a long incubation period, with an annual incidence of 0.5 to 1 case per million individuals. There are three types of CJD: familial (fCJD), acquired (aCJD) and sporadic (sCJD), and this represents the most common form of the disease, approximately 85% of CJD cases[1,4].

Even though the disease is lethal in the absolute number of cases, research with some drugs, such as Quinacrine and Doxycycline, were developed with the aim of trying to increase the survival time of patients with Prion diseases, especially those affected by Creutzfeldt-disease. Jakob in his sporadic form. Quinacrine is a drug that can cross the blood-brain barrier and precisely reach the Central Nervous System (CNS), so it is used to treat cerebral malaria and has also been shown, in vitro, to be potent in the treatment of Human Prion Diseases[7,8]. In vitro and in vivo studies have shown that Doxycycline reverses the resistant PrPsc protease extracted from CJD brains, decreases the infectivity titer in prion-contaminated materials, and prolongs the survival of animals infected with Prion disease[9]. Thus, the two drugs, before being used in clinical trials, were carefully evaluated in studies and, with this, it was possible to slightly understand the relationship of these drugs with the prion and their eventual use in the treatment of human TSEs.

To compose the present study, two articles that evaluated Quinacrine and two that evaluated Doxycycline were chosen. In the study by Collinge et al.[7], participants were responsible for deciding on treatment, so the method of the PRION-1 study is called the "patient preference trial". In it, 84 patients were enrolled at baseline: only 1 agreed to randomization, 38 chose Quinacrine at enrollment, with only 37 receiving the drug, and 68 did not choose Quinacrine, with 1 of them subsequently choosing randomization and 2 of them starting drug administration. Overall, 40 patients received Quinacrine in the study. In the study by Geschwind et al.[8], participants were re-evaluated at months 2, 6, and 12 after the first administration of Quinacrine, those who were re-evaluated at month 2 had the option to continue on study or enter an open-label study with medication dose change. Altogether, 51 individuals with CJD were included in the survival analysis, 28 in the placebo group and 23 in the Quinacrine group.

The study by Haïk et al.[9], was performed in Italy and France and all enrollees were similar with respect to sex, age, and codon 129 genotype. The only difference in selection criteria between countries was that, in Italy, patients had a duration of illness from onset of clinical signs up to 6 months. In this sense, the duration of illness before randomization was longer in the French study compared to the Italian study. In this study, 121 subjects were randomized, 62 in the Doxycycline group and 59 in the placebo group. Varges et al.[10] described that their study consists of two studies: a double-blind randomized phase 2 clinical trial and an observational one, but only the first was included in the present study. In it, 12 patients with sCJD were randomized, 7 in the Doxycycline group and 5 in the control group. An important point of this study is that the patients included had an early stage of CJD.

Among the tests commonly used in the studies, there is the Mini-Mental State Examination (MMSE), whose purpose is to assess the cognitive function of patients, acting as a tracking instrument during the study. This exam allows a complete evaluation in several domains, such as temporal and spatial orientation, immediate and recall memory, among other analyses, and indicates which functions need to be investigated in the evaluated patients[10]. Collinge et al.[7] reported that the MMSE was the most important precursor to choosing or not choosing Quinacrine by patients, that is, it was a relevant test for the development of the study. However, to obtain a definitive diagnosis of the disease, other more specific tests must be used, such as imaging studies, electroencephalography (EEG), analysis of the cerebrospinal fluid, with the identification of the 14-3-3 protein and brain biopsy[1,11,12].

Previous examinations were essential to obtain the characteristics of the population studied and the inclusion or exclusion in the study. Haik et al.[9] adopted as inclusion measures patients who had typical CJD abnormalities on MRI, a typical electroencephalogram (EEG) or a positive CSF test of 14-3-3. In the same sense, for Varges et al.[10], the inclusion criteria were having an MMSE greater than 6 points or a Barthel Index greater than or equal to 20%. Furthermore, the neuropsychological tests performed in this study were important to be able to select patients at an early stage of the disease.

In terms of study time, Collinge et al.[7], reported that the PRION-1 study lasted approximately 113 weeks and had a median follow-up time of patients without death of 16 months. In that study, 34 patients died within 6 weeks of enrollment. The study by Geschwind et al.[8] had a duration of almost 4 years (from April 2005 to January 2009), but the patients were formally followed up until May 2009 and, after that, the last data collection of some patients was obtained until October 2010. In the study by Haïk et al.[9],

the duration was approximately 3 years. In Italy, the study took place between 2007 and 2010 and, in France, between 2009 and 2012, the year in which the study was completed. The randomized study by Varges et al.[10] had a duration of 2 and a half years, and treatment started 3 months after the onset of the disease, with an average duration of 89 days. In view of these analyses, it was found that the duration of the studies was considered relatively fast and that this property is due, in principle, to the fact that CJD is a disease with accelerated and fatal progression.

Among the challenges that arise at some point after the administration of Quinacrine, Collinge et al.[7] emphasizes that some serious adverse effects (SAEs) were reported in 11, but that, overall, only 2 of the 14 AEs were drug-related. The most common findings observed were seizure, hematemesis, hematuria, abdominal wall abscess, delirium, vomiting and aspiration pneumonitis, aspiration pneumonia, abnormal liver function, and abnormal behavior. Geschwind et al.[8] reports that the adverse effects (AE) evidenced between month 2 were similar between the two groups, sample and placebo, and that each group had 3 AEs. Only one SAE (severe gastrointestinal discomfort) was associated with Quinacrine. After that month, other AEs and 6 AEs were reported, but only the change in behavior was listed as possibly due to the drug. Overall, the drug was well tolerated among patients and the two quinacrine studies emphasized that the drug was associated with a high incidence of AEs, most of which were mild and resulted only in dose reduction or discontinuation[6,8].

Varges et al.[10] reported that an AE rate of 70% was observed in the Doxycycline group and 60% in the placebo group, and the AE rate was 40% in both groups. The main reported reactions were mainly dysphagia, respiratory failure, upper and lower airway infections, gastrointestinal disorders, thrombosis and urinary tract infections. Furthermore, Haik et al.[9] reported that in Italy, 11 AEs were reported, 4 in the Doxycycline group and 7 in the placebo group in 7 patients, but they were not drug related. In the French group, AEs were reported in 6 patients (3 in the placebo group and 3 in the Doxycycline group) and that, probably, 4 other patients had other effects. Additionally, the existence of many adverse effects in common between the specific symptoms of CJD and the administration of drugs may contribute to the impossibility of knowing the exact cause of the AEs and AEs reported in the studies.

In terms of mortality, studies carried out with the two drugs did not show favorable results regarding patient survival, although they were, in general, well tolerated by them. Of the 37 patients who chose to receive quinacrine at enrollment in the Collinge et al.[7] and 15 were alive at the last follow-up. In all, 78 (73%) patients died, and although it appears that mortality was lower in those who administered the drug, there was no difference in mortality between the groups after final adjustments. As in the study by Geschwind et al.[8] participants were re-evaluated at month 2, 6, and 12 after the start of the study, it was observed that 13 of 23 subjects who received Quinacrine (57%) and 19 of 28 placebo subjects (68%) survived to month 2, and in addition, after that month, patients who received the drug showed less cognitive decline compared to placebo. At the end of the study, two participants, one in each group, were alive until the last follow-up, but both were receiving life-prolonging measures. Haik et al.[9] reports that, by the end of the study, about 86% of the patients enrolled in the study had died, but that these deaths did not appear to be related to the trial drug. The randomized study by Varges et al.[10] ended with the death of the last patient in the placebo group.

The survival analysis, one of the most relevant points of the studies, corroborated the findings of the randomized part of the study. Studies with Quinacrine showed that there was no significant difference in survival between the group of patients who received the drug and those who did not, and that it did not significantly affect the clinical course of the disease. Geschwind et al.[8] highlights that the hazard ratio shows a survival benefit of placebo over Quinacrine, however this result does not reach statistical significance, however, the Confidence Index (CI) indicates a survival benefit for Quinacrine over placebo. In the studies with Doxycycline, no improvements were observed in the survival of the analyzed patients. However, Varges et al.[10] revealed that the mean survival time after starting treatment with Doxycycline was 95 days, while for the control group it was 33 days, showing an increase in survival in patients who administered the drug. However, an explanation for this finding may be due to the stage of the disease when the treatment started, which, in the Varges study, only included patients in the initial stage of the disease[10,11].

An important point of the work is in relation to the concentrations and the effects of the two drugs in the studied patients. Collinge et al.[7] explains that one of the possible explanations for the lack of success of Quinacrine in the study is that adequate concentrations of the drug were not reached at crucial sites for the antiprion effect, as already evidenced in animal models. However, 4 of the 40 patients who received quinacrine had quinacrine-related toxicity in this study, although they showed a transient improvement in neurological rating scales at one or two visits after initiation of treatment[7].

Geschwind et al.[8] reports that one of the reasons for the failure of the study was the insufficient concentration of Quinacrine at the site where PrPs are accumulated. Haik et al.[9] states that the concentration of the drug used in the brain may not have been sufficient to limit the spread of PrPsc. The prophylactic approach to therapeutic options does not seem to be adequate, since, in the analyzed studies, there was a high incidence of adverse effects, and the administration of drugs did not interfere positively in the survival of patients affected with sCJD.

Although quinacrine did not prolong patient

survival, Geschwind et al.[8] emphasizes that, during the initial two-month phase of the study, the group that received the drug showed less cognitive decline in two predictors, however, no relevant cognitive differences were observed in other tests. It has also been observed that administration of Quinacrine, both in vitro and in vivo, at the outset may reduce the concentration of PrPsc, but continuation of treatment results in selection of strains resistant to the effects of the drugs. In the same sense, Haïk et al.[9] reported that Doxycycline did not show a significant improvement in survival or decrease in CJD progression, the drug was well tolerated by patients and the amount and characteristics of adverse events were similar between the sample and control population. However, Varges et al.[10] reported that a prolonged survival time was observed in patients who received Doxycycline compared to the control group, but this finding may be related to the fact that only patients at an early stage of the disease were included in the study.

Currently, there is no scientific evidence that a drug is able to prevent the progression of CJD, especially its sporadic form. However, in a double-blind, placebo-randomized clinical trial, a reduction in cognitive deterioration, but no effect on survival, was observed in 13 flupirtine-treated patients compared to the control group. In possession of this information, Otto et al.[13] proposed that Flupirtine acts in a neuroprotective manner through the positive regulation of the bcl-2 proto-oncogene and the normalization of the glutathione level[12,13]. Although this neuroprotection had already been recorded in a cell and animal culture, more advanced studies are needed to elucidate the mode of action of Flupirtine in the progression of prion diseases, especially sCJD.

A limitation of the present study was the relative lack of specific information about CJD, since the symptoms and laboratory findings may be related to other types of CJD. Thus, some data are more broadly associated with CJD and its characteristic, without specifying its sporadic form.

Even with the results seen, these studies showed that randomized and appropriate clinical trials can be performed in cases of rare, progressive and fatal neurodegenerative diseases[7,8,9,10]. It is evident that there are many uncertainties regarding therapeutic methods for this comorbidity. However, due to the symptoms and mortality of CJD, as well as the repercussions on the quality of life of the affected individual and his/her family, it is of great importance to formulate larger trials, such as randomized and controlled clinical trials, or prospective cohort studies, with a greater number of patients and reducing research bias.

Due to the rapid progression of the disease, the invariably fatal outcome, the scarcity of tests that detect the early diagnosis and the lack of parameters for monitoring and monitoring Prion diseases, especially CJD with its high prevalence, future drugs must be evaluated through randomized controlled trials or prospectively followed cohort studies. The formulation of more research will help in the analysis of the drug's effect in relation to Prion diseases and will make it possible for a future treatment to be effective to stop the progression of these diseases and to increase the survival of affected patients.

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