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[Intervention Protocol]

Immunomodulatory treatment for amyotrophic lateral sclerosis/motor neuron disease

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the efficacy and harms or adverse events of immunomodulatory therapies in people with ALS compared with a placebo, no additional treatment, or a standard-of-care protocol (with or without riluzole, edaravone, or both).

BACKGROUND

Description of the condition

Motor neuron disease (MND) is a relentlessly progressive fatal neurodegenerative disease with no curative treatment (Del Aguila 2003). MND comprises many clinical subtypes, amyotrophic lateral sclerosis (ALS) being the most common. Most cases of ALS are sporadic but 5% to 10% are familial (Murray 2004). The incidence of ALS varies from region to region and has been found to range from 0.3 per 100,000 per year to 9.9 per 100,000 per year (Doi 2014; Fong 2005; Liu 2018; Marin 2014). MND is more common in men than women (with a male:female ratio between 1.1:1 and 1.9:1). The incidence of ALS increases progressively with age; similarly, the male-to-female ratio has been shown to be higher in the elderly (Doi 2014; Liu 2018; Marin 2014). In the absence of a curative treatment, management remains symptomatic and supportive. Riluzole and edaravone (approved in some countries), the only evidence-based disease modifying treatments to date, at best offer modest survival advantage.

Description of the intervention

Neuroinflammation (activation of the immune system in nervous tissue) has been shown to be associated with motor neuron injury; however, whether neuroinflammation is a primary cause or a consequence of injury is not well understood (Zhao 2013). The roles of innate (natural) and adaptive (acquired) immunity have also been examined, with evidence suggestive of an increase in microglial (specialised immune cell) activity in people with ALS (Corcia 2012; Turner 2004), and corresponding changes in the T helper cell type 1 and type 2 (Th1 and Th2) responses, depending on the stage of ALS. Activated microglia can broadly be classified as classically activated (M1 microglia) and alternatively activated (M2 microglia). M1 microglia activity is cytotoxic in nature and stimulates the production of proinflammatory cytokines (immunoregulatory cytokines that favour inflammation). In ALS mice, a transition from M2 microglial activity (with a corresponding Th2 response) to M1 microglial activity (with a corresponding Th1 response) has been shown to define the change from an early reparative phase of ALS to a late, relentlessly progressive, phase of ALS.

Whether at the level of brain and spinal cord, where microglia are the primary immune cells, or in peripheral immune responses, where Th1 responses and cytokines dominate, there is evidence that immune dysregulation contributes to the pathogenesis of ALS. Immunomodulation therefore represents an attractive treatment target and an option for utilisation in people with ALS. Trials addressing immunomodulation have been few, with heterogeneity both in terms of interventions and outcome measures. Therefore, it remains uncertain whether immunomodulatory treatment in ALS alters the course of this otherwise relentlessly progressive disease.

How the intervention might work

On the basis of previous studies, there is evidence that immune dysregulation is integral to the pathogenesis of ALS. Various pathways and targets that modulate the immune response have been utilised to benefit people with ALS, ranging from nonspecific immune-suppression by drugs (azathioprine, glatiramer acetate) or other interventions (lymphoid irradiation) to more targeted therapy, in the form of NP001 or anakinra (Cudkowicz 2006; Drachman 1994; Gordon 2006; Gordon 2007; Kelemen 1983; Lauria 2015; Maier 2015; Meininger 2009; Meyer 2008; Miller 2015; Stommel 2009). NP001 is an intravenous preparation of purified sodium chlorite that is pH adjusted. It has been shown to decrease proinflammatory activity by downregulating CD16-expressing macrophages (activated white blood cells that kill microorganisms) in the blood of people with ALS (Miller 2014). Anakinra is a recombinant human interleukin-1 receptor antagonist (a protein that inhibits the activity of interleukin-1) that may regulate the inflammatory response in people with ALS via modulation of caspase-1 activity (an enzyme that proteolytically cleaves other proteins) (Dinarello 2012).

Why it is important to do this review

Other than for riluzole and edaravone, there is a marked paucity of evidence-based pharmacological options for the treatment of ALS. The trials published to date have utilised different drugs or interventions, and no more than two studies have reported on the same treatment strategy. Also, the choice of outcome measures and the interval after which these were evaluated has not been consistent. Therefore, there is heterogeneity in terms of the treatment studied and evaluation of outcome measures.

The criteria for the diagnosis of ALS and its assessment have evolved over the past two decades (Brooks 1994; Van den Berg 2019). It is, therefore, important to consider eligibility criteria in light of the extant criteria.

In view of available evidence that immunomodulation could be an effective treatment strategy, it is important to explore and define the current status of immunomodulators in ALS. Combining the data in this systematic review may provide some meaningful conclusions to guide therapy or future research in people with ALS.

OBJECTIVES

To assess the efficacy and harms or adverse events of immunomodulatory therapies in people with ALS compared with a placebo, no additional treatment, or a standard-of-care protocol (with or without riluzole, edaravone, or both).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), quasi-RCTs and cluster-RCTs. We will also include the first arm of cross-over trials, if any. (Quasi-RCTs are studies that employ an approximation of randomisation to allocate participants to treatment groups, e.g. by date of birth, case record number or alternation.) We will include studies reported as full text, those published as abstract only, and unpublished data. We will include trials ineligible for quantitative synthesis, including those terminated early for any reason.

Types of participants

We will include people of any age or sex diagnosed with definite or probable ALS/MND according to established criteria, such as the revised El Escorial World Federation of Neurology criteria (Brooks 2000), or revised Airlie House criteria (Van den Berg 2019). For the sake of homogeneity, we will not consider variants of ALS and types of MND (other than well-defined ALS) for evaluation. Regarding studies published with a mixed population, we will include the ALS

subpopulation (if appropriately defined and all related outcomes have been reported); as applicable; evidence from the given study may or may not be downgraded for indirectness in the summary of findings table.

Types of interventions

We will include trials of immunomodulatory therapy, either in the form of medication or an intervention, such as plasmapheresis with immunosuppression, total lymphoid irradiation, celecoxib, glatiramer acetate, minocycline, thalidomide, the interleukin-1 antagonist anakinra, NP001, pentoxifylline, or any other immunomodulatory drug or intervention. Comparison interventions will be placebo, no additional treatment, or a standard-of-care protocol (with or without riluzole, edaravone, or both). We will include a trial if different immunomodulatory therapies or different routes of intervention were involved, if we identify any such studies. We will allow co-interventions, provided that they have been administered to each group equally.

We will not include cell-based therapies in the review, as these are the subject of a published Cochrane Review (Abdul Wahid 2019).

Types of outcome measures

The outcomes listed here are not eligibility criteria for this review, but are outcomes of interest within whichever studies are included. We will report outcomes at six months and 12 months.

Primary outcomes

- Functional impairment, assessed using a functional rating scale: change in Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) (Cederbaum 1999; Kaufmann 2005)
- Overall survival

Secondary outcomes

1. Muscle strength, assessed by manual muscle testing Medical Research Council (MRC) grade
2. Respiratory function, assessed by forced vital capacity (FVC) - change from baseline will be prioritised over final score
3. Change in compound muscle action potential (CMAP) and neurophysiological index (NI)
4. Quality of life (QoL), assessed by measures such as ALS Assessment Questionnaire (ALSAQ-40), Short-Form 36 (SF-36), Profile of Mood State (POMS), etc. as reported
5. Structural or functional changes in serial magnetic resonance imaging (MRI) of the brain
6. Serious adverse events
7. Adverse events resulting in withdrawals

Search methods for identification of studies

Electronic searches

The Information Specialist will identify trials from the following resources:

- Cochrane Neuromuscular Specialised Register (via Cochrane Register of Studies (CRS) Web), which is maintained by the Information Specialist for the Group;
- Cochrane Central Register of Controlled Trials (CENTRAL; via CRS Web);
- MEDLINE (via Ovid SP; 1946 to search date; Appendix 1);
- Embase (via Ovid SP; 1974 to search date);
- US National Institutes for Health Clinical Trials Registry, ClinicalTrials.gov (ClinicalTrials.gov);
- WHO International Clinical Trials Registry Portal (ICTRP; apps.who.int/trialsearch/).

We will translate and adopt the MEDLINE search strategy for other resources.

We will search all databases from their inception to the present, and will impose no restriction on language of publication or publication status.

Searching other resources

We will search reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information.

Data collection and analysis

Selection of studies

One author (BPS) will import all search results into Covidence. Two review authors (HSM and HCAE) will independently screen titles and abstracts of references retrieved by the search and code them as 'yes', 'maybe' (retrieve) or 'no' (exclude). We will retrieve potentially eligible full-text study reports or publications for closer assessment. Two review authors (HSM and NK) will independently screen the full-text reports and identify studies for inclusion, and identify and record reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (SC). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA 2020 flow diagram (Page 2021) and characteristics of excluded studies table.

Data extraction and management

Two review authors (HSM and HCAE) will extract study characteristics from included studies. We will use a data extraction form, which we will pilot on at least one study in the review.

We will collect information on study design and setting, participant characteristics (including disease severity and age), study eligibility criteria, details of the intervention(s) given, the outcomes assessed, the source of study funding and any conflicts of interest stated by the investigators (Higgins 2019).

Two review authors (NK and SC) will independently extract outcome data from included studies. If a study does not report outcome data in a usable way, we will note this in the characteristics of included studies table. We will resolve disagreements by consensus or by involving a third person (RKG). One review author (HSM) will transfer data into Review Manager (RevMan Web 2020). A second author (NK) will check the outcome data entries. Another review author (CAM) will spot-check study characteristics for accuracy against the trial report.

When reports require translation, the translator will extract data directly using a data extraction form, or review authors will extract data from the translation provided. Where possible, a review author (NK) will check numerical data in the translation against the study report.

Assessment of risk of bias in included studies

Two review authors (HSM and RK) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (BPS or CAM). We will assess the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other biases, including design-specific biases

We will grade each potential source of bias as high, low or unclear, and provide a quote from the study report together with a justification for our judgment in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for survival may be very different than for a participant-reported quality of life scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

It is expected that not all studies or trials will report the primary outcome measure in the form of ALSFRS-R; ALSFRS-R measures the person's functional capabilities that can be compared over a period of time. This will especially be true for studies published before 1999, the year when the ALSFRS-R was developed. Since there is no common unit of conversion for the outcome measures, for quantitative synthesis we will only consider trials published after 1999 that report ALSFRS-R; we will evaluate outcome measures reported otherwise narratively.

We will analyse dichotomous data as risk ratios (RRs) and continuous data as a mean differences (MDs), or standardised mean difference (SMDs) for results across studies with outcomes that are conceptually the same but measured in different ways. We will use a 95% confidence interval as a measure of estimated uncertainty for all outcome measures. We will enter data presented as a scale with a consistent direction of effect. While we will measure most primary and secondary outcomes as continuous data, we will measure overall survival as dichotomous data. Serious adverse events or adverse events requiring withdrawal might be reported as dichotomous data as well as continuous data and measured accordingly.

Unit of analysis issues

The unit of analysis will be the individual person. We will only consider the first period data of a cross-over trial. The unit of analysis will be family, group, or ALS team for cluster-RCTs.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting (Higgins 2019).

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is available as an abstract only). Where this is not possible, and assumptions about the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial unexplained heterogeneity we will report it and explore possible causes by prespecified subgroup analysis.

We will use the rough guide to interpretation as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study biases (Higgins 2019).

Data synthesis

We will use a random-effects model in anticipation of heterogeneity in trial characteristics, and perform a sensitivity analysis (as detailed in the subsequent section).

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. If the review includes comparisons that cannot be included in the same analysis, we will report the results for each comparison separately. This may include one or more of the following: the control may be in the form of a placebo, no treatment, standard of care (non-immunomodulator), other drug of same class of immunomodulatory treatment or any other route of same drug. We intend to pool all immunomodulators and do a subgroup analysis by the type of immunomodulator.

We will present data that cannot be included in a meta-analysis narratively in tables, following guidance in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2021).

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Type of immunomodulator received
2. Type of comparator (standard of care)
3. Mode of delivery of drug
4. Severity of ALS (change in ALSFRS-R (progression rate): slow (< 0.47) versus fast (> 1.11); Libra 2016))
5. Sex, if reported

We will use the following outcomes in subgroup analyses (as reported in the trials).

1. Functional impairment assessed using a functional rating scale (change in ALSFRS-R)
2. Overall survival
3. Muscle strength, assessed by MRC grade
4. Respiratory function, assessed by FVC
5. Change in CMAP and NI
6. QoL
7. Structural or functional changes in serial MRI of the brain
8. Serious adverse events
9. Adverse events resulting in withdrawals

We will use the formal test for subgroup interactions in Review Manager (RevMan Web 2020).

Sensitivity analysis

We plan to carry out the following sensitivity analyses.

1. Repeat the analysis excluding unpublished studies (if there are any).
2. Repeat the analysis excluding studies at high risk of bias, e.g. as a result of missing data (as identified during the review process).

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table for each comparison using the following outcomes.

1. Functional impairment, assessed using a functional rating scale (change from baseline to 6 months): ALSFRS
2. Functional impairment, assessed using a functional rating scale (change from baseline to 12 months): ALSFRS
3. Overall survival at 6 months
4. Overall survival at 12 months
5. Muscle strength assessed by manual muscle testing (at six months): MRC grade
6. Respiratory function, assessed by FVC (change from baseline to six months)
7. Serious adverse events

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of body of evidence (studies that contribute data for the prespecified outcomes). We will use methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* using GRADEproGDT software (GRADEpro GDT; Schunemann 2019). Briefly, the certainty of the evidence is graded into four levels: high, moderate, low, and very low. We will justify all decisions to downgrade or upgrade the certainty of evidence of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

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APPENDICES

Appendix 1. MEDLINE (OvidSP) draft strategy

Database: Ovid MEDLINE(R) ALL <1946 to 8 May 2020>

Search Strategy:

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1 randomized controlled trial.pt.

2 controlled clinical trial.pt.

3 randomized.ab.

4 placebo.ab.

5 drug therapy.fs.

6 randomly.ab.

7 trial.ab.

8 groups.ab.

9 or/1-8

10 exp animals/ not humans.sh.

11 9 not 10

12 exp Motor Neuron Disease/MND/motor Neurone disease

13 (moto*1 neuron*1 disease*1 or moto?neuron*1 disease*1 or nmd).mp.

14 ((Lou Gehrig*1 adj5 syndrome*1) or (Lou Gehrig*1 adj5 disease)).mp.

15 (Amyotrophic Lateral Sclerosis or ALS).mp.

16 or/12-15

17 exp immunologic factors/

18 exp adjuvants, immunologic/

19 exp Immunosuppressive Agents/

20 exp Immunomodulation/

21 Plasmapheresis/

22 Immunoglobulins, Intravenous/

23 Immunoglobulins/

24 Lymphatic Irradiation/

25 Celecoxib/

26 Glatiramer Acetate/

27 Minocycline/

28 Thalidomide/

29 Interleukin 1 Receptor Antagonist Protein/

30 Pentoxifylline/

31 (immunologic or immunosuppress* or immunomodulat* or plasmapheresis or immunoglobulin*1 or (lymph* adj irradiation) or celecoxib or glatiramer or minocycline or thalidomide or anakinra or NP001 or pentoxiphylline or Pentoxifylline).mp.

32 intravenous immunoglobulin*.mp.

33 ivig.tw.

34 intra venous immunoglobulin*.tw.

35 intravenous immune globulin*.tw.

36 or/17-35

37 11 and 16 and 36

38 remove duplicates from 37

WHAT'S NEW

Date	Event	Description
3 July 2022	Amended	Editorial correction to Declarations of interest section and change to formatting of an author's name

HISTORY

Protocol first published: Issue 6, 2022

CONTRIBUTIONS OF AUTHORS

HSM: Conception of the review, co-ordination of the review, developing first draft of protocol, assessment of the certainty of the body of evidence, writing of the review.

BPS: Conception of the review, protocol development, assessment of risk of bias in the included studies, writing of the review before final submission.

NK: Protocol development and proofreading of protocol, full-text screening of studies, collection of outcome data for the review, assessment of the certainty of the body of evidence, interpretation of data and writing of the review.

RKG: Protocol development, proofreading of protocol, conceptualised the review question, resolving disagreement in data extraction, and approval of final version of the review.

RK: Advised on the protocol, assessing risk of bias of included studies, analysis of data, approval of the final version of the review.

HCAE: Protocol development, screening of abstracts and full texts, and approval of final version of review.

SC: Advised on protocol development, extraction of outcome data of included studies.

CAM: Protocol development, proofreading of protocol, resolving disagreements in risk of bias assessment of included studies, approval of final version of review.

GV: Protocol development, design of the review, interpretation of data and approval of final version of review.

DECLARATIONS OF INTEREST

HSM: none known

BPS: none known

NK: none known

RK: none known

HCAE: Professor Emsley is employed by Lancaster University and Lancashire Teaching Hospitals NHS Foundation Trust. He is currently seconded (via Lancaster University, for one session per week) to the Innovation Agency (North West Coast Academic Health & Science Network in his capacity as Deputy Clinical Lead for the Connected Health Cities project). He has a number of external professional roles, including as Stroke Advisory Group member for the Association of British Neurologists. He periodically advises on national guideline documents for neurology and stroke. He has a number of pending research grant applications. He accepted sponsorship by Medtronic (registration fee) to attend a Stroke meeting in London in 2017.

SC: Dr Chhetri has received funding from George Barton Motor Neurone Disease Trust, a charity trust, to undertake research in Motor Neuron Disease. Travel and accommodation arrangements were made by GlaxoSmithKline pharmaceuticals for Dr. Chhetri to attend investigators' meeting on monoclonal antibody drug trial in Amyotrophic Lateral Sclerosis (Ozanezumab, GSK1223249: GlaxoSmithKline).

CAM: none known

GV: Since October 2017 I have been employed by Cochrane Response, an evidence services unit operated by the Cochrane Collaboration. Cochrane Response, a division of the Cochrane Collaboration, has been contracted by the European Association of Neurology (EAN) to conduct this review.

RKG: I received honoraria/royalties for writing clinical summaries/articles for the following publications: Medlink Neurology, UpToDate Wolters Kluwer.

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External sources

- NIHR, MNDA, UK

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