Rituximab and Cyclophosphamide as Second-line Immunotherapy for Autoimmune Encephalitis

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Background

- Autoimmune encephalitis (AE) is an inflammatory disorder of the brain that entails the presence of antibodies (Abs) against intracellular neuronal antigens, neuronal surface antigens or glial antigens, or there may be an absence of detectable Abs.
- While both first-line immunotheraphy, comprising steroids, intravenous globulin (IVIG) and plasma exchange, and second-line immunotherapy consisting of rituximab, cyclophosphamide or combinations thereof, are well delineated, there is still a lack of evidence-based guidelines on choosing the second-line immunotherapy strategy, accounting for heterogeneity in medical practice.

Research question

The PICO question was the following:
For adult patients (at least 18 years old) with AE, does treatment with rituximab (375 mg/ once a week for at least 4 weeks or 1 g infused twice, 2 weeks apart), cyclophosphamide (750 mg/ once a month for at least 4 months), or both regimens combined, as opposed to absence of intervention, lead to a better clinical outcome (decrease in the mRS of at least 1 point from onset, or absence of relapses, i.e. exacerbation of previous symptoms or the occurrence of new symptoms.

Identification of studies

We performed a systematic search using the PubMed and Web of Knowledge databases (studies published prior to June 2021).

- For the search in PubMed we used the following query:

("paraneoplastic syndromes, nervous system"[MeSH Terms] OR "autoimmune encephalitis"[Text Word] OR "limbic encephalitis"[Text Word]) AND ("Cyclophosphamide"[MeSH Terms] OR "Cyclophosphamide"[Text Word] OR "Rituximab"[MeSH Terms] OR "Rituximab"[Text Word]).

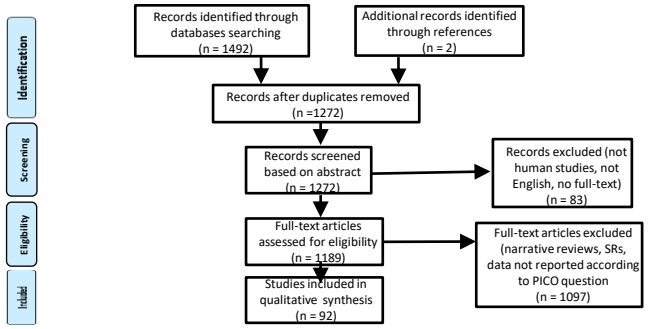
- In Web of Knowledge we performed an advanced search:

#1 ts=rituximab; #2 ts=cyclophosphamide; #3 ts=(autoimmune near/0 encephaliti*); #4 ts=(limbic near/0 encephaliti*); #5 ts=(paraneoplastic near/0 cerebellar near/0 degeneration); #6 ts=(opsoclonus near/0 myoclonus); #7 ts=opsoclonus; #8 ts=(opsoclonus-myoclonus); #9 ts=(opsoclonus near/0 myoclonus); #10 ts=SPS; #11 ts=stiff-limb; #12 ts=stiff-person; #13 ts=stiff-man; #14 ts=morvan; #15 ts=isaacs*; #16 ts=(sensory near/0 neuronopathy); #17 ts=Lambert-Eaton; #18 ts=hu; #19 ts=yo; #20 ts=cv2/crmp5; #21 ts=cv2; #22 ts=crmp5; #23 ts=sox1; #24 ts=pca2; #25 ts=amphiphysin; #26 ts=ri; #27 ts=ma2; #28 ts=tr; #29 ts=KLHL11; #30 ts=Kelch-like; #31 ts=ANNA-2; #32 ts=ANNA-1; #33 ts=zic4; #34 ts=VGCC; #35 ts=(voltage-gated near/0 calcium near/0 channels); #36 ts=gad; #37 ts=gad65; #38 ts=NMDA; #39 ts=NMDAR; #40 ts=NMADRE; #41 ts=lgi1; #42 ts=caspr2; #43 ts=gaba; #44 ts=gabaa; #45 ts=gabab; #46 ts=gabaar; #47 ts=gababr; #48 ts=ampa; #49 ts=ampar; #50 ts=mGluR1; #51 ts=mGluR5; #52 ts=dppx; #53 ts=iglon5; #54 ts=glyr; #55 ts=glycine; #56 ts=GFAP; #57 ts=neuromyotonia; #58 ts=(Isaac near/0 syndrome); #59 ts=PERM; #60 ts=(paraneoplastic near/0 neurologic); #61 ts=(#1 OR #2) AND (#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60)

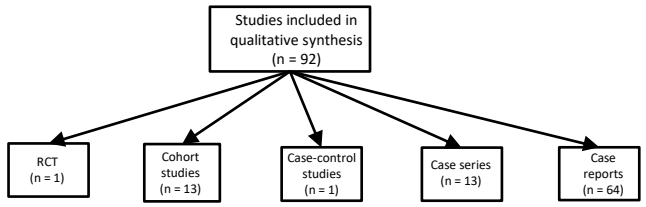
We merged the results from the 2 databases.

- We also attempted to include unpublished data (e.g. meeting abstracts not available online) for a comprehensive search of available evidence.

Data extraction and quality appraisal



Evidence profile (GRADEPro)



- **Level of certainty: LOW** – cohort studies and case-control downgraded once due to imprecision; case series / case reports downgraded twice due to impresision and risk of bias; there was one randomised control trial (RCT)[2] whose own level of certainty was moderate, having downgraded once for imprecicision;

- No downgrading for inconsistency, indirectness or publication bias;
- No large effect, no plausible confounding, no dose-response gradient.

Summary of judgements

1. Problem: Probably yes
AE can be a highly debilitating disease largely affecting young people and prompt initiation of treatment is paramount. Failure of first-line immunotherapy must prompt immunosuppression with a second-line agent.

2. Desirable effects: Moderate
- no. of participants: 160
- certainty of evidence (GRADE): LOW
- additional considerations: had the studies not been underpowered, the anticipated desirable effects would increase

3. Undesirable effects: Small
- reported mild adverse events: infusion-related reactions (e.g. headache, dizziness, chest discomfort), neutropenia, rash, pruritus (2 studies)[2-3]
- reported serious adverse events: haemorrhagic cystitis (1 study)[4], severe neutropenia, severe lymphopenia and infection (1 study)[5], leading to discontinuation of intervention

4. Certainty of evidence: Low

5. Values: Probably no important uncertainty or variability
No systematic review (SR) was conducted on how patients value the main outcome, however there was informed consent of patients included in studies; in addition, medical clinical judgement was important in critical clinical setting.

6. Balance of effects: Probably favors the intervention

7. Resources required: no economic evaluation was performed

8. Cost effectiveness: no cost-effectiveness evaluation was performed

9. Equity: no SR was conducted on health equity

10. Acceptability: Probably yes
Although no SR was conducted on acceptability of the intervention by stakeholders, it is likely to be well accepted.

11. Feasibility: Probably yes
Although no SR was conducted on feasibility, we consider that the intervention is probably feasible to implement.

Recommendations and rate overall quality

TYPE OF RECOMMENDATION: Conditional recommendation for the intervention

Determination of direction and strength of recommendation was based on the best available evidence, the quality of evidence and the balance between desirable and undesirable effects. The certainty of evidence overall was low.

- To increase the level of evidence, RCTs and head-to-head studies on second-line immunotherapy options are needed, as well as SRs on values, acceptability, equity, resources and cost effectiveness.
- Consideration of different treatment regimens is also important in relation to the outcome. For example, lower dosages of rituximab (e.g. 100 mg IV once per week for 4 consecutive weeks) were found to be effective in achieving a good clinical outcome[6].

REFERENCES: 1. Graus F. et al A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016; 15(4): 391-404. 2. Dalakas M.C. et al A double-blind, placebo-controlled study of rituximab in patients with stiff person syndrome. Ann Neurol 2017; 82(2):277-277. 3. Byun J-I. et al Effect of immunotherapy on seizure outcome in patients with autoimmune encephalitis: a prospective observational registry study. PLoS Med 2016; 13(5):e1002045. 4. Halbert R. K. Anti-N-Methyl-D-Aspartate-Receptor Encephalitis: A Case Study. J Neurosci Nurs 2016; 48(3):170-173. 5. Titulaer M. J. et al Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013; 12(2):157-165. For a complete list of included studies, contact: antonia.lefter@yahoo.com