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Immunomodulatory interventions for focal epilepsy (Review)

Panebianco M, Walker L, Marson AG

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[Intervention Review]

Immunomodulatory interventions for focal epilepsy

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ABSTRACT

Background

This is an updated version of an original Cochrane Review published in 2013 (Walker 2013).

Epilepsy is a common neurological disorder affecting 0.5% to 1% of the population. Pharmacological treatment remains the first choice to control epilepsy. However, up to 30% of people do not respond to drug treatment, and therefore do not achieve seizure remission. Experimental and clinical evidence supports a role for inflammatory pathway activation in the pathogenesis of epilepsy which, if effectively targeted by immunomodulatory interventions, highlights a potentially novel therapeutic strategy.

Objectives

To assess the efficacy and tolerability of immunomodulatory interventions on seizures, adverse effect profile, cognition, and quality of life, compared to placebo controls, when used as additional therapy for focal epilepsy in children and adults.

Search methods

For the latest update, we searched the following databases on 11 November 2021: Cochrane Register of Studies (CRS Web) and Medline (Ovid) 1946 to 10 November 2021. CRS Web includes randomised or quasi-randomised, controlled trials from PubMed, EMBASE, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Specialized Registers of Cochrane Review Groups including Epilepsy. We placed no language restrictions. We reviewed the bibliographies of retrieved studies to search for additional reports of relevant studies.

Selection criteria

Randomised placebo-controlled trials of add-on immunomodulatory drug interventions, in which an adequate method of concealment of randomisation was used. The studies were double-, single- or unblinded. Eligible participants were children (aged over 2 years) and adults with focal epilepsy.

Data collection and analysis

We used standard methodological procedures expected by the Cochrane Collaboration.

We assessed the following outcomes.

1. 50% or greater reduction in seizure frequency.
2. Seizure freedom.
3. Treatment withdrawal for any reason.
4. Quality of life.
5. Adverse effects.

We used an intention-to-treat (ITT) population for all primary analyses, and we presented results as risk ratios (RRs) with 95% confidence intervals (95% CI).

Main results

We included three randomised, double-blind, placebo-controlled trials on a total of 172 participants. All trials included children and adults over two years of age with focal epilepsy. Treatment phases lasted six weeks and follow-up from six weeks to six months. One of the three included trials described an adequate method of concealment of randomisation, whilst the other two trials were rated as having an unclear risk of bias due to lack of reported information around study design. Effective blinding of studies was reported in all three trials. All analyses were by ITT. One trial was sponsored by the manufacturer of an immunomodulatory agent and therefore was at high risk of funding bias.

Immunomodulatory interventions were significantly more effective than placebo in reducing seizure frequency (risk ratio (RR) 2.30, 95% confidence interval (CI) 1.15 to 4.60; 3 studies, 172 participants; moderate-certainty evidence). For treatment withdrawal, there was insufficient evidence to conclude that people were more likely to discontinue immunomodulatory intervention than placebo (RR 1.04, 95% CI 0.28 to 3.80; 3 studies, 172 participants; low-certainty evidence). The RR for adverse effects was 1.16 (95% CI 0.84 to 1.59; 1 study, 66 participants; low-certainty evidence). Certain adverse effects such as dizziness, headache, fatigue, and gastrointestinal disorders were more often associated with immunomodulatory interventions. There were little to no data on cognitive effects and quality of life. No important heterogeneity between studies was found for any of the outcomes. We judged the overall certainty of evidence (using the GRADE approach) as low to moderate due to potential attrition bias resulting from missing outcome data and imprecise results with wide confidence intervals.

Authors' conclusions

Immunomodulatory interventions as add-on treatment for children and adults with focal epilepsy appear to be effective in reducing seizure frequency. It is not possible to draw any conclusions about the tolerability of these agents in children and adults with epilepsy. Further randomised controlled trials are needed.

PLAIN LANGUAGE SUMMARY

Immunomodulatory interventions (treatments that target the immune system) for focal epilepsy

Key messages

Immunomodulatory interventions are treatments that target the immune system.

Focal epilepsy is characterised by seizures arising from a specific area of the brain.

Immunomodulatory interventions were significantly more effective than placebo in reducing seizure frequency in children and adults with focal epilepsy.

What is epilepsy?

Epilepsy is a common neurological condition affecting approximately 50 million people worldwide. Focal epilepsy is characterised by seizures arising from a specific area of the brain. Approximately one-third of patients with epilepsy continue to have seizures despite treatment with antiepileptic drugs. Therefore, the development of effective new therapies for the treatment of epilepsy is of considerable importance. Recently, it has been suggested that the immune system and how it responds to injury may play an important role in this process. As such, immunomodulatory interventions - treatments that target the immune system - may represent a therapeutic approach for focal epilepsy.

What did we want to find out?

We wanted to find out if treatments that target the immune system are better than placebo, in children and adults with focal epilepsy. We also wanted to find out if these treatments are safe.

What did we do?

We searched for studies that looked at treatments that target the immune system in children and adults with focal epilepsy. We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

Treatments that target the immune system may be effective in reducing seizure frequency in adults with focal epilepsy. These treatments are more often associated with an increase in adverse effects such as dizziness, headache, fatigue, and gastrointestinal disorders, but it is not possible to draw any conclusions about the safety of these agents in children and adults with focal epilepsy.

What are the limitations of the evidence?

We are moderately confident in the evidence due to missing outcome data and imprecise results from the studies. Further high-quality research is needed to fully evaluate the efficacy and tolerability of immunomodulatory interventions.

How up to date is this evidence?

The evidence is up-to-date to November 2021.

Summary of findings 1. Immunomodulatory interventions compared with placebo for focal epilepsy

Immunomodulatory interventions compared with placebo for focal epilepsy

Patient or population: people with focal epilepsy

Intervention: immunomodulatory interventions

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Immunomodulatory interventions				
Seizure freedom						No data available
50% or greater reduction in seizure frequency - ITT analysis	155 per 1000	357 per 1000 (178 to 713)	RR 2.30 (95% CI 1.15 to 4.60)	172 (3 studies)	⊕⊕⊕⊖ **Moderate**[1,2]	RR > 1 indicates outcome is more likely in immunomodulatory interventions group.
Adverse events of glucocorticoids and immunosuppressive drugs	647 per 1000	751 per 1000 (543 to 1029)	RR 1.16 (95% CI 0.84 to 1.59)	66 (1 study)	⊕⊕⊖⊖ **Low**[1,2]	RR > 1 indicates outcome is more likely in immunomodulatory interventions group.
Treatment withdrawal	52 per 1000	54 per 1000 (15 to 198)	RR 1.04 (95% CI 0.28 to 3.80)	172 (3 studies)	⊕⊕⊖⊖ **Low**[1,2]	RR > 1 indicates outcome is more likely in immunomodulatory interventions group.
Allergic reactions						No data available
Cognitive effects						No data available
Quality of life						No data available

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[1] Downgraded once for imprecision: number of events (< 400) did not meet the optimal information size.
[2] Downgraded once for inconsistency: significant statistical heterogeneity was detected (P < 0.10).

BACKGROUND

This review is an update of the original Cochrane Review previously published in 2013 (Walker 2013).

Description of the condition

Epilepsy is a chronic neurological condition characterised by recurrent seizures. Seizures result from excessive electrical discharge within a population of hyperexcitable neurons. Focal epilepsy is characterized by seizures arising from a specific area of the brain; it occurs as a consequence of a neurological insult. Many such insults, including neuroinfection, neurotrauma, and stroke, are known to be associated with a high risk of both blood-brain barrier disruption. Focal seizure symptoms reflect the region of brain from which they originate. When there is no associated impairment in consciousness, it is called a simple focal seizure, and when it is associated with impairment in consciousness, it is called a complex focal seizure. When a focal seizure becomes generalised, it is referred to as a focal seizure with secondary generalisation (Falco-Walter 2018).

Electroencephalogram (EEG) and neuroimaging - computed tomography scan (CT scan) and magnetic resonance imaging (MRI) - are performed in the early stage of the diagnostic evaluation of focal epilepsy.

Epilepsy is a severe neurological condition affecting approximately up to 70 million people worldwide. With an incidence of 50/100,000 patient years and a prevalence of 700/100,000, epilepsy accounts for more than 0.5% of the total global burden of disease. Each year, 2.4 million people are diagnosed with epilepsy, contributing to 20.6 million disability-adjusted life years lost (Trinka 2023). Focal epilepsy constitutes the most common seizure type, representing up to 61% of the epilepsy population (Gupta 2017).

Unfortunately, anti-seizure medications (ASMs) fail to achieve seizure remission in approximately 30% of epilepsy sufferers (Kwan 2000). Despite the emergence of many new ASMs and alternative treatments over the last 20 years, including the use of neuromodulatory treatment (vagus nerve stimulation) used as an adjunctive therapy (Panebianco 2015; Panebianco 2022), the prevalence of treatment-resistant epilepsy remains high.

This review focusses on children (over 2 years of age) and adults with focal epilepsy.

Description of the intervention

Possible immunomodulatory drug interventions include glucocorticoids in all formations and immunosuppressant drugs.

Recent studies have shown that neuroinflammation may both precipitate and sustain seizures, implying that inflammation may be involved not only in epileptogenesis, but also in the development of the drug-resistant profile (Marchi 2011).

Glucocorticoids inhibit the transcription of several pro-inflammatory cytokines produced by human monocytes and macrophages, including IL-1β, IL-6, IL-12, TNFα, or GM-CSF and down-regulate the expression of chemokines like IL-8, RANTES, and MCP-1. Glucocorticoids inhibit the synthesis of several inflammatory mediators implicated in inflammation through an inhibitory effect on enzyme production. The inducible form of nitric oxide synthase (iNOS), upregulated by pro-inflammatory cytokines, is a target of glucocorticoids in a murine macrophage cell line (J774). They also inhibit induction of the gene coding for cyclooxygenases-2 (COX-2) in rat alveolar macrophages. Thus, glucocorticoids limit amplification of inflammation by repressing pro-inflammatory macrophage activation and additionally induce anti-inflammatory monocyte and macrophage populations, actively promoting resolution of inflammation (Ehrchen 2019).

Immunosuppressive agents inhibit or prevent activity of the immune system by a number of different mechanisms. This can include antimetabolic activity, cytokine signalling/production interference, and monoclonal/polyclonal antibodies directed towards identified antigens. Immunosuppressive drugs include: antimetabolites, are chemicals that inhibit the use of a metabolite, which is another chemical that is part of normal metabolism; macrolides are antibacterials used for control of infection;caspase-1 inhibitors, interleukin-1 (IL-1) receptors antagonist, tumour necrosis factor (TNF/TNF)-alpha inhibitors are drugs that help stop inflammation with immunomodulatory effects; intravenous immunoglobulins are a mixture of antibodies used to treat a wide range of medical conditions; mammalian target of rapamycin (mTOR) signalling pathway interference is a key regulator of many cellular processes including cell metabolism, growth, proliferation, survival and immunity; monoclonal antibodies are produced from a cell lineage made by cloning a unique white blood cell; polyclonal antibodies are a complex mixture of several antibodies that are usually produced by different B-cell clones of an animal (see Table 1).

How the intervention might work

The mechanisms underlying "drug resistance" remain unclear. Data from experimental epilepsy models and resected human brain tissue support the involvement of innate immune system activation and consequent inflammation in epilepsy (Vezzani 2005a; Vezzani 2005b). Initial insights arose from studies of the pro-inflammatory cytokine interleukin (IL)-1β (IL-1β), its target, interleukin-1 receptor type 1 (IL-1R1), and its naturally occurring competitive antagonist, interleukin-1β receptor antagonist (IL-1RA) (Vezzani 2011). In rodents, both chemically and electrically-induced seizures cause upregulation of all three (IL-1β, IL-1R1, and IL-1RA) in the brain (Vezzani 2008). Sustained elevation of IL-1β long after the initial seizure event, suggests that sustained, localised inflammation may be important in epilepsy (De Simoni 2000). A similar pattern of over-expression is observed in human epileptogenic brain tissue in association with a variety of pathologies including hippocampal sclerosis, focal cortical dysplasia, and tuberous sclerosis (Boer 2008; Crespel 2002; Ravizza 2006; Ravizza 2008). Also, in human studies, seizures have been associated with significantly increased levels of the pro-inflammatory cytokine interleukin-6 in blood and cerebrospinal fluid (CSF) (Lehtimaki 2004; Peltola 1998). Furthermore, a highly pro-inflammatory cytokine profile (high IL-6, low IL-1RA, low IL-1RA/IL-1β ratio) has been identified in the plasma of people with epilepsy (Hulkkonnen 2004). Lastly, in addition to over-expression arising as a consequence of seizures, targeting IL-1β can modulate susceptibility to seizure-inducing stimuli. IL-1RA has direct anticonvulsant activity following intracerebral administration and transgenic mice that over-express this protein in astrocytes (a subtype of glial cells that make up the majority of cells in the CNS have reduced seizure susceptibility (Auvin 2010; Vezzani 2000)). Similarly, IL-1R1 knock-out mice (a laboratory

mouse in which researchers have inactivated, or "knocked out," an existing gene by replacing it or disrupting it with an artificial piece of DNA) exhibit reduced sensitivity to chemically induced seizures (Vezzani 2000).

The innate immune response exists to protect the CNS from insult and, ordinarily, the process is halted by removal of the injurious stimuli. However, as a result of incompletely understood processes, this important biological switch-off mechanism may become compromised, resulting in persistent microglial activation and cytotoxicity. In this way, the inflammatory response may well contribute to the development of recurrent seizures and, furthermore, may be implicated in a person's response to ASMs. Targeting brain inflammation may represent a novel therapeutic strategy for epilepsy.

The direct mechanism underlying how immunomodulatory drugs might improve epileptic seizures is still incompletely understood. However, considering the emerging data regarding the role of inflammation in epileptogenesis, it is not unreasonable to assume that suppression of inflammation following an epileptogenic insult may reduce the resultant epileptic focus and reduce future seizures.

Why it is important to do this review

Pharmacoresistance and ongoing, debilitating seizures remain the greatest challenge in the management of epilepsy. Understanding the contribution that inflammation plays in pathogenesis and, furthermore, the role that immunomodulatory drugs play in limiting this development, may allow us to target therapies at particularly susceptible patient groups - post-CNS injury - to prevent the development of pharmacoresistant seizures.

OBJECTIVES

To assess the efficacy and tolerability of immunomodulatory interventions on seizures, adverse effect profile, cognition, and quality of life, compared to placebo, when used as additional therapy in focal epilepsy in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies that met all the following criteria:

1. Randomised controlled studies in which an adequate method of concealment of randomisation was used.
2. Double-blind, single-blind, and unblinded trials: parallel-group, placebo-controlled trials.
3. No minimum treatment period.

Types of participants

Children (over 2 years of age) and adults of either gender with focal epilepsy (i.e. experiencing simple focal, complex focal, or secondarily generalised tonic-clonic seizures). These included people with a recent diagnosis as well as those with chronic focal epilepsy.

Types of interventions

1. The experimental interventions included glucocorticosteroids or immunosuppressants by oral, intravenous, intramuscular, or subcutaneous route taken in addition to ASMs treatment. Glucocorticosteroids include dexamethasone, hydrocortisone, methylprednisolone, and prednisolone. Anti-cytokine treatments include caspase-1 inhibitors (VX-765), and interleukin-1 receptor antagonists (Anakinra). Immunosuppressive drugs included: abetimus, adalimumab, afutuzumab, afelimomab, anakinra, aritox, aselizumab, atorolimumab, azathioprine, basiliximab, belimumab, bertilimumab, biolimus A9, cedelizumab, certolizumab pegol, ciclosporin, clenoliximab, daclizumab, deforolimus, dorlixizumab, ecluzimab, efalizumab, elsilimomab, erlizumab, etanercept, everolimus, faralimomab, fontolizumab, galiximab, gantenerumab, gavilimomab, golimumab, gomiliximab, gusperimus, infliximab, inolimomab, intravenous immunoglobulins, ipilimumab, keliximab, lebrikizumab, leflunomide, lenalidomide, lerdelimumab, lumiliximab, maslimomab, mepolizumab, metelimumab, methotrexate, morolimumab, mycophenolic acid, muromonab-CD3, natalizumab, ocrelizumab, omalizumab, otelixizumab, pascolizumab, pegsunercept, pexelizumab, pimecrolimus, reslizumab, rituximab, rovelizumab, ruplizumab, siplizumab, sirolimus, tacrolimus, talizumab, temsirolimus, teneliximab, teplizumab, teriflunomide, thalidomide, toralizumab, tremelimumab, tocilizumab, ustekinumab, vapaliximab, vepalimomab, visilizumab, zotarolimus, zanolimumab, and zolimomab (see Table 1).
2. Control interventions included placebo, no additional treatment, or another immunomodulatory drug intervention analysed separately.

Types of outcome measures

Primary outcomes

1. Seizure freedom, defined as the proportion of patients that achieve complete seizure cessation during the treatment period.
2. 50% or greater reduction in seizure frequency during the treatment period, compared to baseline seizure frequency.

Secondary outcomes

1. All adverse effects secondary to glucocorticoids, including:
   a. diabetes mellitus;
   b. impaired glucose tolerance;
   c. infection;
   d. weight gain;
   e. osteoporosis;
   f. menstrual irregularity;
   g. euphoria/psychosis;
   h. glaucoma; and
   i. cataracts.
2. All adverse effects secondary to long-term immunomodulation, including:
   a. infection; and
   b. induction of malignancy.
3. Cognitive side effect, including confusion, delirium, drowsiness, and sedation.

4. Allergic reactions
5. Other serious side effects, as defined by the European Medicines Agency (EMEA 1995):
   a. results in death;
   b. is life-threatening;
   c. requires inpatient hospitalisation or prolongation of existing hospitalisation;
   d. results in persistent or significant disability/incapacity;
   e. congenital anomaly/birth defect; and
   f. requires intervention to prevent permanent impairment or damage.
6. Participants that experience any adverse effect.
7. Treatment withdrawal: due to intolerable side effects or lack of efficacy or a combination.
8. Quality of life (QOL): there is no consensus on which instruments should be used to assess quality of life, so we tabulated the results rather than combine them in a meta-analysis.

Search methods for identification of studies

Electronic searches

Searches were run for the original review in July 2012. Subsequent searches were run in May 2013, April 2015, August 2017, and August 2019.

For the latest update, we searched the following databases on 11 November 2021:

1. Cochrane Register of Studies (CRS Web), using the search strategy set out in Appendix 1.
2. MEDLINE (Ovid 1946 to 10 November 2021), using the search strategy set out in Appendix 2.

CRS Web includes randomised or quasi-randomised, controlled trials from PubMed, EMBASE, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Specialised Registers of Cochrane Review Groups including Epilepsy. In MEDLINE (Ovid) the coverage end date always lags a few days behind the search date.

We imposed no language restrictions. We tailored searches to individual databases, and adapted from those used in the previous review.

Searching other resources

For the original review and for this update, we checked reference lists of reviews and retrieved articles for additional studies, and performed citation searches on key articles. We contacted experts in the field for unpublished and ongoing studies.

Data collection and analysis

Selection of studies

For this update, two review authors (LW and MP) independently screened all the titles and abstracts of publications identified by the searches to assess their eligibility. We excluded publications that did not meet the criteria at this stage. We then reviewed the full text of eligible citations for inclusion and reached consensus on the selection of studies and the final list of studies. We resolved any disagreements by discussion with a third author (AGM). Two review authors (LW and MP) independently extracted data and assessed the risk of bias for included studies; again, we resolved disagreements by mutual discussion.

Data extraction and management

We extracted the following data for each trial, using a data extraction form:

Participant and demographic information

1. Total number of participants allocated to each treatment group
2. Age
3. Sex
4. Epilepsy classification/seizure type
5. Aetiology
6. Duration of epilepsy
7. Age at onset of first non-febrile convulsion
8. Seizure frequency prior to randomisation
9. Number and types of ASMs previously taken
10. Number and types of ASMs currently taking
11. Comparability of groups at baseline
12. Presence of neurological signs at baseline
13. Electroencephalography results at baseline
14. Neuroimaging results at baseline

Methods and trial design

1. Criteria/classification system used to diagnose epilepsy
2. Inclusion and exclusion criteria
3. Method of randomisation
4. Method of allocation concealment
5. Method of blinding
6. Stratification factors
7. Number of participants allocated to each group

Intervention and controls

1. Intervention given to control group
2. Duration of immunosuppressant given
3. Interval between doses of immunosuppressants
4. Total number of corticosteroid infusions and total number of days per course
5. Duration of treatment period

Follow-up data

1. Duration of follow-up
2. Reasons for incomplete outcome data
3. Drop-out or loss to follow-up rates
4. Methods of analysis (intention-to-treat, per protocol, worst-case/best-case scenario analysis)

Outcomes

We recorded the number of participants who experienced each outcome (see Types of outcome measures) per randomised group, and contacted authors of studies for any missing information.

Assessment of risk of bias in included studies

Two review authors (LW and MP) independently assessed the risk of bias for each trial, using the Cochrane risk of bias tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We discussed and resolved disagreements. We completed a risk of bias table for each included study in Review Manager (Review Manager 2020). We rated all included studies as having a low, high, or unclear (indicating lack of information or uncertainty over the potential for bias) risk of bias on six domains applicable to randomised controlled trials: randomisation method, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting, and other sources of bias. There was no disagreement in assessing the risk of bias between the review authors.

We evaluated the following characteristics:

1. Was the allocation sequence adequately generated?
2. Was there sufficient blinding of participants, personnel and outcome assessors?
3. Were incomplete outcome data adequately addressed (yes/no)?
4. Free of selective reporting?
5. Free of other bias?

Measures of treatment effect

We analysed the primary outcome of seizure freedom and seizure reduction as a binary outcome and presented it as a risk ratio (RR). We also analysed secondary outcomes, including treatment withdrawal, as binary outcomes and presented RR. We planned to present adverse effects, cognitive effects and quality of life as secondary outcomes, but due to the limited amount of data available for cognitive effects and quality of life, we have reported these outcomes narratively.

Unit of analysis issues

We did not identify any unit of analysis issues.

Dealing with missing data

We sought missing data by contacting the study authors. We analysed data according to intention-to-treat analysis (ITT) in those instances of missing data due to drop-out or lost to follow-up. Studies where data required to calculate outcomes of interest were missing would have been followed up by writing to the trial author, if necessary. The potential implications of missing data (e.g. no outcome obtained, lack of compliance, ineligibility) are addressed in the Discussion section.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important participants factors between studies (e.g. age, gender, epilepsy classification, seizure types, seizure frequency, epilepsy duration), interventions (administration method, dosage, duration, co-interventions) and trial design issues (study duration, randomisation, allocation concealment, and blinding methods). We examined statistical heterogeneity ($P < 0.10$), with a fixed-effect model. Had we found heterogeneity (> 50%), we had planned to use a random-effects model for the analysis.

Assessment of reporting biases

We requested protocols for all included studies to enable a comparison of outcomes of interest. If we suspected outcome reporting bias for any included study, we planned to further investigate using the ORBIT matrix system (Kirkham 2010). We planned an examination of asymmetrical funnel plots to establish publication bias, but we were not able to assess this due to the small number of studies included in the review.

Data synthesis

We used a fixed-effect model meta-analysis to synthesise the data. We measured the effect of each comparison on our preset primary and secondary outcomes, if data were available. Comparisons we expected to carry out included usual treatment plus immunomodulatory interventions versus usual treatment plus placebo. Our preferred estimator for all binary outcomes was the Mantel-Haenzsel Risk Ratio (RR). For the outcomes of 50% or greater reduction in seizure frequency, treatment withdrawal, and adverse effect, we used 95% confidence intervals (CI). For cognitive effects and quality of life, we narratively summarised the data from the studies. For the efficacy outcome (50% or greater reduction in seizure frequency), we undertook primary intention-to-treat (ITT) analysis: we assumed participants who did not complete follow-up or with inadequate seizure data, to be non-responders. To test the effect of this assumption, we undertook the following sensitivity analyses; we performed ITT analysis when this was reported by the included studies.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses according to the different age groups of participants (children younger than 17 years versus adults).

Sensitivity analysis

We intended to carry out a sensitivity analysis if we found peculiarities between study quality, characteristics of participants, interventions, and outcomes (assessment of risk of bias in included studies).

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to summarise findings, as detailed in the GRADE Handbook (Schűnemann 2013). We imported data into GRADEpro GDT software from Review Manager 2020 to create a summary of findings table for the main comparison of the review (immunomodulatory interventions compared to placebo). We assessed the certainty of evidence for the following outcomes: seizure freedom, 50% or greater reduction in seizure frequency, adverse events, treatment withdrawal, allergic reactions, cognitive effects, and quality of life.

We assessed the primary outcomes, 50% or greater reduction in seizure frequency, and the secondary outcomes, adverse events, and treatment withdrawal, to provide an overall certainty of evidence judgement based on the GRADE approach, which was then included in Summary of findings 1. This information is of importance for healthcare decision-making and considers eight important criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, presence of plausible confounding that will change effect, and dose-response gradient).

We use the overall certainty of evidence judgements to guide our conclusions.

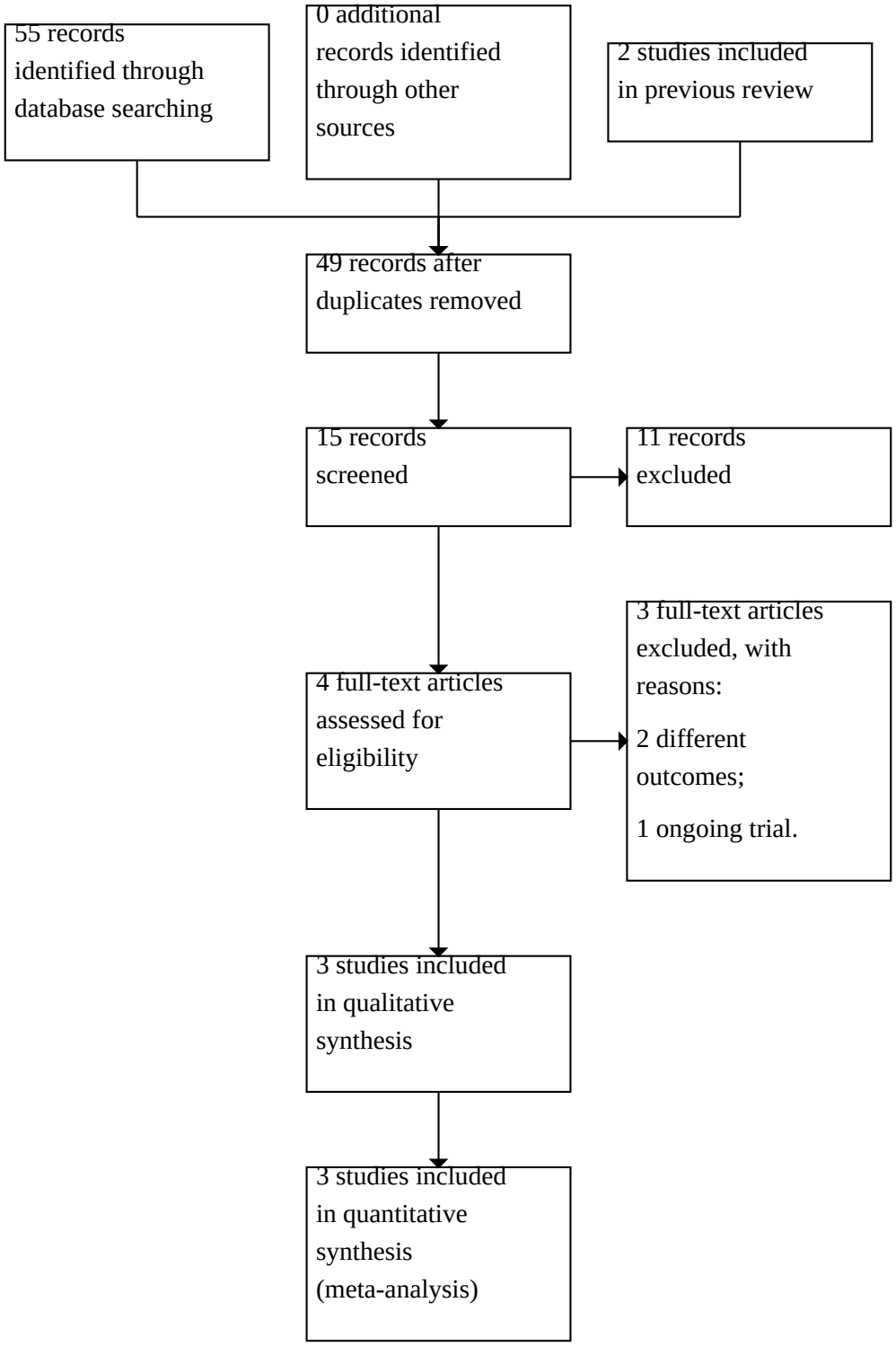
RESULTS

Description of studies

Results of the search

The search carried out on 11 November 2021 identified 55 records from the databases outlined above. After we removed duplicates, we screened 15 records for inclusion in the review. We excluded 11 studies at this point, and requested 4 full-text articles to assess eligibility. We contacted the authors of these studies for more information, providing their contact details were available. Following this, we excluded 2 studies (Patel 2021; Zhao 2021). We also found one ongoing clinical trial (CTRI/2021/02/030974). One trial was suitable for inclusion (French 2021). Search results and details on included and excluded studies are summarised in Figure 1.

Figure 1.



During a previous search, conducted in 2013, reviews authors identified two randomised controlled studies investigating the use of immunomodulatory interventions for focal epilepsy (French 2012; Van Rijckevorsel-Harmant 1994). One trial was listed as an ongoing clinical trial (NCT01545518), and one trial as awaiting classification (Simko 1997), because no sufficient information was available.

In total, we included three studies (French 2012; French 2021; Van Rijckevorsel-Harmant 1994).

Included studies

See Characteristics of included studies.

Van Rijckevorsel-Harmant 1994 was a randomised, double-blind, placebo-controlled trial of intravenous immunoglobulins (IVIG) for the treatment of epilepsy, that fulfilled the inclusion criteria of the previous review. However, only a subgroup of participants had focal epilepsy, and it included both adults and children (with no separate analysis by age). A total of 61 participants were randomly assigned to receive an active compound (at either 100, 250, or 400 mg/kg per infusion) or placebo in addition to their current ASMs. The infusion schedule consisted of four infusions in the first week followed by further single infusions in the second, third, and sixth week. The study included an optional booster at the end of the six months if the investigators felt this was indicated. . In terms of seizure frequency, statistical analysis of changes was only performed where data were available for both the preceding 12 months (average) and at the study conclusion. Seizure frequency was the total number of seizures, daily, irrespective of type, occurring in the preceding 12 months.

French 2012 was a phase two, randomised, double-blind, placebo-controlled study in adults to evaluate the efficacy and safety of VX-765 in subjects with treatment-resistant focal epilepsy. Participants were randomly assigned to receive an active compound (900 mg VX-765 three-times-daily, n=48) or placebo (three-times-daily, n=12) in addition to their current ASMs. The primary endpoint of the study was the safety and tolerability of VX-765. However, some secondary efficacy outcomes were included.

French 2021 was a phase two, randomised, double-blind, placebo-controlled study in adults to evaluate the efficacy and safety of natalizumab as adjunctive therapy for subjects with drug-resistant epilepsy. Participants with ≥ 6 seizures during the 6-week baseline period were randomised 1:1 to receive natalizumab 300 mg IV or placebo every 4 weeks for 24 weeks. Randomisation was stratified based on the presence or absence of structural etiology for focal epilepsy and seizure frequency (< 24 and ≥ 24 seizures) and during the baseline period. An electronic seizure diary was used to collect daily records of seizures. Primary efficacy outcome was change from baseline in log-transformed seizure frequency, with a predefined threshold for therapeutic success of 31% relative reduction in seizure frequency over the placebo group. Secondary efficacy endpoints included the proportion of participants with > 50% reduction from baseline in seizure frequency; proportion of participants free from seizures; percentage of seizure-free days gained compared with baseline, and the proportion of participants with an inadequate treatment response, defined as modification of ASMs after week 12 of the placebo-controlled period or discontinuation of treatment after the active run-in period due to lack of efficacy. One person did not receive 300 mg of natalizumab due to IV complications.

Excluded studies

See Characteristics of excluded studies

In this update, we excluded two studies because they did not measure our outcomes of interest (Patel 2021; Zhao 2021). One trial was listed as an ongoing clinical trial because no results have so far been published (CTRI/2021/02/030974).

In the previous review, some excluded studies could not be assessed due to the presence of confounding conditions. Barbaro 2009 evaluated the use of steroids only in conjunction with radiosurgery in the presence of brain oedema. Barile-Fabris 2005 evaluated the use of immunomodulatory agents in the treatment of neurological manifestations of an underlying autoimmune condition.

Risk of bias in included studies

See Figure 2 and Figure 3 for a summary of the risk of bias in each included study. We allocated each study an overall rating of low, high or, unclear risk of bias. See below for specific domain ratings.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

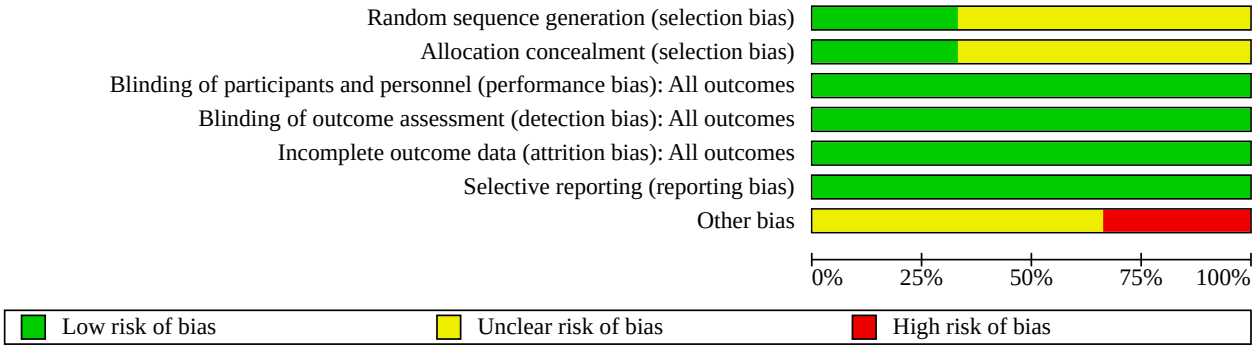
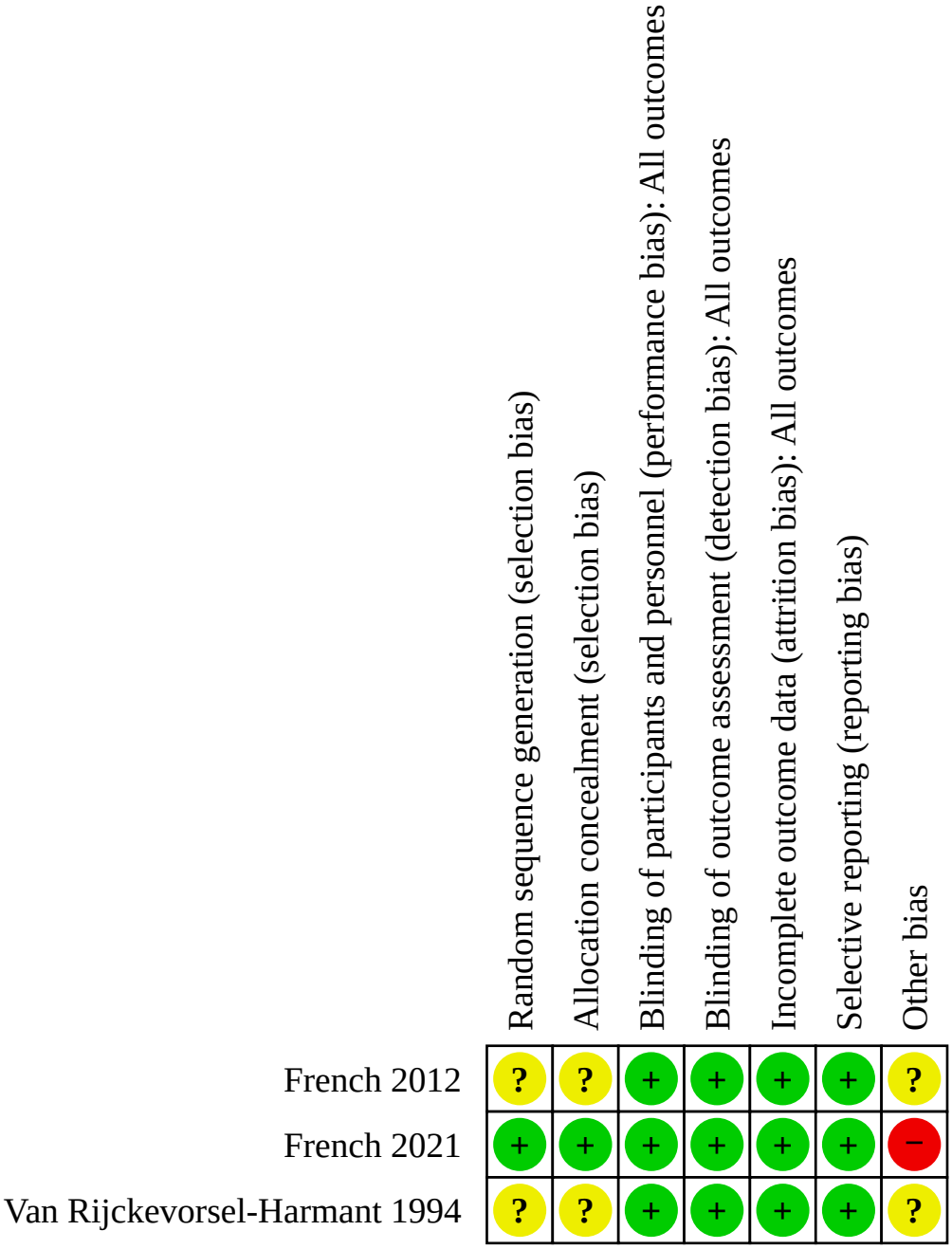


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

One study provided details regarding randomisation of participants, therefore we judged it to be at low risk of selection bias (French 2021). In contrast, we assessed the other two studies as having an unclear risk of selection bias because the participants were randomly assigned to treatment or placebo, but no further information was given (French 2012; Van Rijckevorsel-Harmant 1994).

With regard to allocation concealment, one included study described using an interactive response technology and was judged to be at low risk of selection bias (French 2021). We rated the other two included studies as unclear risk of selection bias as methods used for allocation concealment were not reported (French 2012; Van Rijckevorsel-Harmant 1994).

Blinding

We rated all three studies as having a low risk of performance and detection bias because participants, parents, and investigators were adequately blinded by matching placebo (French 2012; French 2021; Van Rijckevorsel-Harmant 1994). Van Rijckevorsel-Harmant 1994 used a placebo which they specified was "otherwise the same as the verum"; the investigators were aware of the dosage group but were unaware of the substance infused; the external assessors (neurologists) were completely blinded to the therapy received.

Incomplete outcome data

We rated all three included studies as having a low risk of attrition bias as minimal missing data were reported; either intention-to-treat (ITT) analysis was employed, or there were no concerns of missing data having an effect on the overall outcome estimate (French 2012; French 2021; Van Rijckevorsel-Harmant 1994). In the Van Rijckevorsel-Harmant 1994 study, one patient had to stop infusions due to possibly related adverse effects (vomiting) but it is not clear whether this individual was included in the final analysis. The analysis of all participants and of the focal epilepsy subgroup was performed with the exclusion of three participants (all within the IVIG group). The exclusions occurred for the following reasons: one patient dropped out for unknown reasons (100 mg/kg group), one patient had continuous focal motor seizures (250 mg/kg group) from the beginning and one patient had unaccountable seizures after baseline (100 mg/kg). In the French 2012 study, one patient discontinued treatment due to adverse events during the study and was in the VX-765 treatment group. In the French 2021 study, one person did not receive treatment due to IV complications.

Selective reporting

We assessed that all included studies were at low risk of reporting bias (French 2012; French 2021; Van Rijckevorsel-Harmant 1994). Despite not supplying a trial protocol, all three studies reported results for all the outcomes measures prespecified in the method section of their respective publications.

Other potential sources of bias

We rated two included studies as unclear risk of bias for this domain because information was unavailable (French 2012; Van Rijckevorsel-Harmant 1994). One study was sponsored by Biogen, the manufacturer of natalizumab; we rated this trial as having a high risk of funding bias (French 2021).

Effects of interventions

See: **Summary of findings 1** Immunomodulatory interventions compared with placebo for focal epilepsy

See: Summary of findings 1

Primary outcome

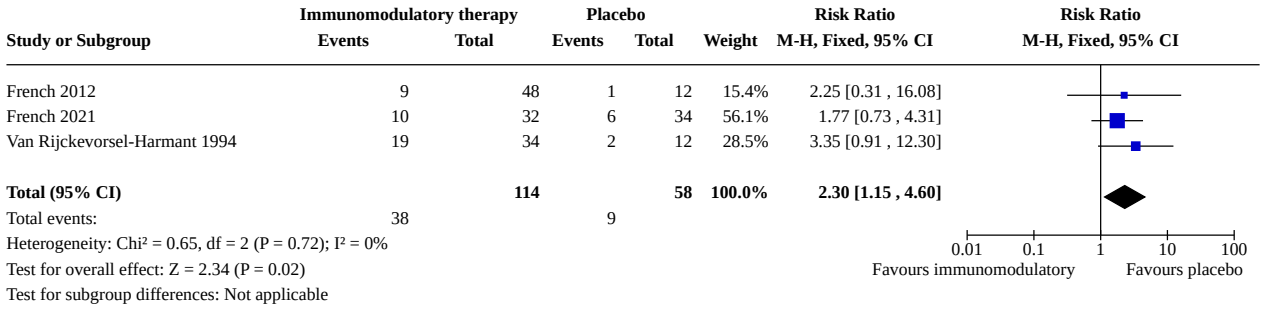
Seizure freedom

None of the included studies measured this outcome.

50% or greater reduction in seizure frequency

Participants were labelled as responders if they achieved a 50% or greater reduction in daily seizure frequency at six months (the time point at which the included studies measured this outcome). At six months, intention to treat (ITT) analisys showed a significant improvement in favour of immunomodulatory interventions added to regular ASM compared to placebo (RR 2.30, 95% CI 1.15 to 4.60; Analysis 1.1; Figure 4). Separate dose results for the different groups were not reported.

Figure 4. Forest plot of comparison: immunomodulatory interventions versus placebo, outcome 1.1: 50% responder.

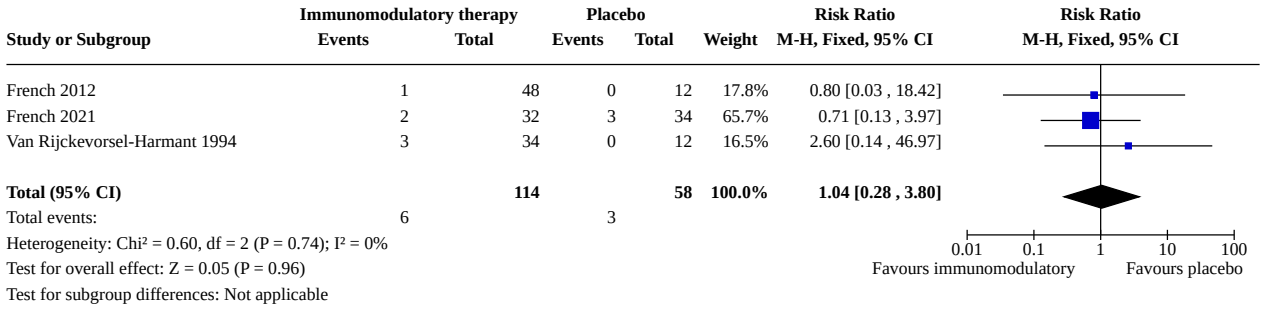


Secondary outcomes

Treatment withdrawal

The overall RR for treatment withdrawal for any reason was 1.04 (95% CI 0.28 to 3.80); thus there was insufficient evidence to conclude that participants given immunomodulatory interventions were more likely to discontinue treatment than those given a placebo (Analysis 1.2; Figure 5).

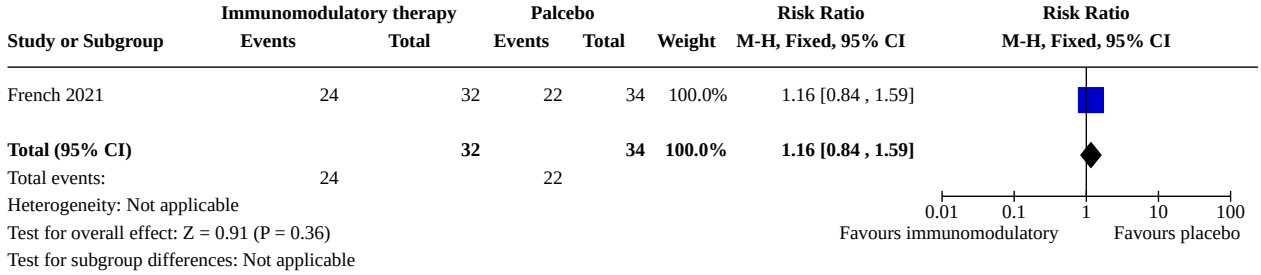
Figure 5. Forest plot of comparison: immunomodulatory interventions versus placebo, outcome 1.2: treatment withdrawal.



Adverse effects

In French 2021, the RR for any adverse effects was 1.16 (95% CI 0.84 to 1.59; Analysis 1.3; Figure 6). The most common were: headache, dizziness, falls, back pain, arthralgia, nausea, contusion, fatigue, blurred vision, vomiting, and anaemia. No serious adverse effects occurred during the treatment period. In French 2012, immunosuppressive drugs were more often associated with an increase in adverse effects such as dizziness, headache, fatigue and gastrointestinal disorders. In Van Rijckevorsel-Harmant 1994, a single participant in the IVIG group had to cease infusions due to vomiting. Overall, it is not possible to draw any conclusions about the safety of glucocorticoids and immunosuppressive agents in adults with epilepsy.

Figure 6. Forest plot of comparison: immunomodulatory interventions versus placebo, outcome 1.3: any adverse effects.



Allergic reactions

Data relating to allergic reactions were not reported.

Cognitive effects

Data relating to cognitive side effects were not reported.

Quality of life assessment

Van Rijckevorsel-Harmant 1994 measured patient and family perspectives as part of the global blind assessment. ITT analysis showed a significant improvement in the IVIG-treated group with refractory epilepsy compared to placebo (RR 3.21, 95% CI 1.10 to 9.36, P = 0.033).

DISCUSSION

Summary of main results

We included in a meta-analysis three randomised, double-blind, placebo-controlled trials on a total of 172 participants. All studies included people with focal epilepsy. Overall, the age ranged from 2 to 75 years. One study included both adults and children without separate analysis. Treatment phases lasted six weeks and follow-up from six weeks to six months.

The overall risk ratio (RR) for reduction in seizure frequency of 50% or more compared to placebo was 2.30 (95% confidence interval (CI) 1.15 to 4.60; 3 studies, 172 participants; moderate-certainty evidence), indicating that immunomodulatory interventions were significantly more effective than placebo in reducing seizure frequency. No data were available for seizure freedom.

The RR for treatment withdrawal compared to placebo was 1.04 (95% CI 0.28 to 3.80; 3 studies, 172 participants; low-certainty evidence); therefore there was insufficient evidence to conclude that participants were more likely to discontinue immunomodulatory intervention than placebo. Data from only one study reported adverse effects: RR 1.16 (95% CI 0.84 to 1.59; 66 participants; low-certainty evidence). Certain adverse effects such as dizziness, headache, fatigue and gastrointestinal disorders were more often associated with immunomodulatory interventions. Data relating to allergic reactions and cognitive effects were not reported. The limited data available precluded any conclusions about quality of life. No significant heterogeneity between studies was found for any of the outcomes.

Overall completeness and applicability of evidence

Immunomodulatory interventions as an add-on treatment for adults with focal epilepsy, appear to be effective in reducing seizure frequency. It is not possible to draw any conclusions about the safety of these agents in adults with epilepsy. Caution is required when translating the results of clinical trials into everyday practice, since participants in trials are a highly selected population who may be more motivated, and are closely followed and monitored. Conversely, participants who are uncooperative and non-compliant, who are likely to have adverse effects and reap fewer benefits, are excluded. The duration of the studies included in this review was insufficient to detect changes in cognition or long-term adverse effects.

Quality of the evidence

We assessed the studies with regard to risk of bias. Overall, one study was at low risk of bias and two studies at unclear risk of bias due to lack of reported information around study design. Effective blinding of studies was reported in all studies. We rated all the included studies at low risk of bias for incomplete outcome data due to the ITT analyses undertaken by the study authors. We used the GRADE approach to rate the certainty of evidence for each outcome, which is presented in Summary of findings 1. We judged the overall certainty of the evidence as low to moderate due to potential attrition bias resulting from missing outcome data and imprecise results with wide confidence intervals.

Potential biases in the review process

Although all protocols were requested, the time frames in which the majority of the studies were conducted made retrieval of all of these difficult. This lack of information could lead to potential bias.

Agreements and disagreements with other studies or reviews

We found no reviews or published information on the use of immunomodulator interventions as add-on therapy for focal epilepsy.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review prove that the addition of immunomodulatory treatment to people with focal epilepsy could substantially improve the course of the disease in some people. It is not possible to draw any conclusions about the safety of these agents in children and adults with epilepsy.

Implications for research

There is a growing amount of animal research suggesting that it might be useful to evaluate the efficacy of immunomodulatory drug interventions for the treatment of epilepsy in humans. None of the existing clinical research is of sufficient quality or size to answer this question. Further high-quality research, including large, well-conducted, randomised controlled clinical trials with adequate follow-up beyond six months, are required before a definite conclusion can be reached concerning the efficacy, safety, and tolerability of immunomodulatory interventions in people with epilepsy. Studies should systematically evaluate and report adverse events. The search identified two ongoing clinical trials in this area (CTRI/2021/02/030974; NCT01545518), therefore a future review is certainly warranted.

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The following people conducted the editorial process for this protocol:

- Managing Editor (provided editorial guidance to authors, edited the protocol, conducted editorial policy checks): Rachael Kelly
- Information Specialist (conducted electronic literature searches): Graham Chan
- Copy Editor (copy editing and production): Lindsay Robertson.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

French 2012

Study characteristics	
Methods	Phase 2, randomised, double-blind, placebo-controlled study of VX-765 in subjects with treatment-resistant focal epilepsy.
Participants	N = 60 participants. Inclusion criteria: 1. Males or females aged 18 to 64 (inclusive) years with a body mass index between 18 and 35 (kg/m2) 2. Subjects with a diagnosis and history of treatment-resistant focal-onset epilepsy and are taking 1 to 4 stable doses of concomitant anti-epileptic drugs at the time of screening period 3. Subjects must have had at least 1 EEG consistent with focal epilepsy 4. Must have had at least 6 focal-onset seizures and a seizure free period of no more than 3 weeks during baseline period 5. Subjects with stable medical conditions may be included (at the discretion of the principal investigator) Exclusion criteria: 1. Subjects with a history of nonepileptic, transient alterations in consciousness (e.g. metabolic, structural, and post-traumatic or pseudo seizures) 2. Pregnant or lactating females or those unwilling to use contraception 3. Those who have a history of status epilepticus in the past 12 months before the screening visit 4. Subjects whose seizure frequency cannot be quantified

French 2012 *(Continued)*

	5. Subjects who have a significant medical illness including kidney, liver, pulmonary, or gastrointestinal disease; or unstable or poorly controlled conditions such as hypertension, diabetes, or angina pectoris, as judged by the investigator 6. Subjects with clinically significant psychiatric illness or had an active suicidal plan/intent, thoughts, or attempt 7. Subjects with clinically significant laboratory abnormalities during the screening visit/baseline period, as judged by the investigator 8. Subjects with active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) 9. Subjects with positive drug screen at screening or during the baseline period (excluding any allowed prescribed medications) and/or a history of alcoholism or drug addiction within past 2 years 10. Subjects on felbamate with fewer than 18 months of continuous felbamate exposure at the time of the screening visit or with significant adverse reactions to felbamate 11. Subjects treated with vigabatrin fewer than 2 years prior to the screening visit or who have a prior history of treatment with vigabatrin without a documented stable examination by an ophthalmologist or neuro ophthalmologist of the visual field within the 2 years prior to the screening visit 12. Subjects treated with any systemic immunosuppressant as defined in the protocol 13. Subjects who experienced a symptomatic viral, fungal, or bacterial infection requiring systemic treatment within 7 days prior to the first dose of study drug 14. Subjects with a current or prior history of illness precluding them from immunomodulatory therapy 15. Subjects who have participated in earlier VX-765 clinical studies and received at least 1 dose of study drug
Interventions	Patients received 6 weeks of treatment with VX-765 or placebo following a 6-week baseline period to monitor seizure frequency. Patients continued to receive standard antiepileptic drugs throughout the study, in addition to VX-765 or placebo. 48 subjects received 900 mg of VX-765 3-times-daily and 12 people received placebo 3-times-daily
Outcomes	Primary outcome: adverse events. Secondary outcomes: 1. Percent reduction in seizure rate 2. Percent of patients with a 50% or greater reduction in seizure frequency 3. Percent of patients who were seizure-free in the last two weeks of treatment.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly assigned to treatment or placebo. However, no further information is given.
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel were blinded to the treatment group.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was double-blind with investigators blinded to which treatment was received.
Incomplete outcome data (attrition bias)	Low risk	1 participant discontinued treatment due to adverse events during the study and was in the VX-765 treatment group.

French 2012 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	The protocol is unavailable but it appears that all expected and pre-specified outcomes were reported.
Other bias	Unclear risk	None detected.

French 2021

Study characteristics	
Methods	Phase 2, randomised, double-blind, placebo-controlled study of natalizumab as adjunctive therapy in subjects with drug-resistant epilepsy. The study was conducted at 31 sites across the United States from March 2018 to January 2020.
Participants	N = 66 participants. Inclusion criteria: Participants aged 18 to 75 years were eligible for enrolment if they had a clinical diagnosis of focal epilepsy, and had experienced ≥ 6 seizures during the baseline period with no more than 21 consecutive seizure-free days, and been on a stable regimen of 1 to 5 ASMs during the 4 weeks before the screening visit and throughout the baseline period. Seizures type included focal aware seizures with motor signs, focal impaired awareness seizures, and focal to bilateral tonic-clonic seizures.
Interventions	Participants received either placebo or natalizumab 300 mg IV in a 1:1 ratio once every 4 weeks for 24 weeks. The study consisted of a 6-week prospective baseline period followed by a double-blind, placebo-controlled period lasting 24 weeks. Following week 24, participants had the option of continuing in a 24-week open-label period.
Outcomes	Primary outcome: change from baseline in log-transformed seizure frequency from weeks 8 to 24 of the placebo-controlled period, where seizure frequency was defined as the number of seizures per 28 days. Secondary outcomes: proportion of participants with ≥ 50% reduction from baseline in seizure frequency; proportion of participants free from seizures; percentage of seizure-free days gained compared with baseline, and the proportion of participants with an inadequate treatment response, defined as modification of ASMs after week 12 of the placebo-controlled period or discontinuation of treatment after the active run-in period due to lack of efficacy.
Notes	The ClinicalTrials.gov registration number is NCT03283371

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed using interactive response technology.
Allocation concealment (selection bias)	Low risk	Randomisation was performed using interactive response technology and was stratified based on the presence or absence of structural etiology for focal epilepsy and seizure frequency (< 24 or ≥ 24 seizures) during the baseline period.

French 2021 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and personnel were blinded to the treatment groups.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was double-blind with investigators blinded to which treatment was received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant did not receive natalizumab 300 mg due to IV complications.
Selective reporting (reporting bias)	Low risk	Protocol unavailable but it appeared that all expected and pre-specified outcomes were reported.
Other bias	High risk	This study was sponsored by Biogen, the manufacturer of natalizumab.

Van Rijckevorsel-Harmant 1994

Study characteristics	
Methods	Prospective, randomised, add-on, double-blind, placebo-controlled trial including a 6-week treatment period and follow-up to 6 months total study time.
Participants	N = 61 participants. Inclusion criteria: 1. West syndrome, Lennox-Gastaut syndrome or early myoclonic encephalopathy 2. Refractory epilepsy of greater than 1 year duration with seizure frequency greater than once weekly. Exclusion criteria: 1. Any form of neoplasia 2. Progressive or expansive cerebral disorders (except Rasmussen syndrome) 3. Features of severe renal insufficiency (serum creatinine > 3 mg/100 ml) 4. Known intolerance of blood products; seropositivity to HIV 1 and 2 5. Known chromosomal abnormality Age range: 2 to 51 years IVIG 100 mg/kg N =14; IVIG 250 mg/kg N = 14; IVIG 400 mg/kg N = 15; placebo N = 18 Mean age: IVIG 100 mg/kg 26.2 years; IVIG 250 mg/kg 24.6 years; IVIG 400 mg/kg 24.4 years; placebo 18.5 years Race: Caucasian. Sex: total 42 male, 19 female: IVIG 100 mg/kg 11 male, 3 female; IVIG 250 mg/kg 10 male, 4 female; IVIG 400 mg/kg 10 male, 5 female; placebo 11 male, 7 female Types of seizures: focal epilepsy Mean duration of epilepsy (years): IVIG 100 mg/kg 19.44 years; IVIG 250 mg/kg 15.33 years; IVIG 400 mg/kg 16.33 years; placebo 12.54 years

Van Rijckevorsel-Harmant 1994 *(Continued)*

Interventions	7-S native immunoglobulins prepared from standard polyvalent gamma globulins, fractionated from a pool of 1000 plasma donors screened for seronegativity towards hepatitis A, B and C viruses as well as HIV 1 and 2. Doses allocated at 100, 250, or 450 mg/kg per infusion. Infusion schedule: 1st week 4 infusions followed by once a week in the 2nd, 3rd and 6th weeks. Placebo consisting of 2% human albumin solution.
Outcomes	1) 50% reduction in mean number of seizures per day between baseline (4 weeks prior to 1st infusion) and 6 months following first infusion. 2) Global blind evaluation providing a rating (markedly, slightly or not improved) which includes reduction in seizure frequency in addition to seizure severity, evolution of EEGs, interictal status and the perception of the patient, family and nursing staff. Adverse events.
Notes	The study included both adults and children with separate analyses. The study included both patients diagnosed with epilepsy syndromes immediately from diagnosis (West, Lennox Gastaut Syndrome, and early myoclonic epilepsy) and chronic drug refractory epilepsy. The aetiology of the epilepsy groups is likely to be distinctly different. All 3 patients that were excluded were from the active treatment (IVIG) group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were randomly assigned to treatment or placebo. However, no further information is given.
Allocation concealment (selection bias)	Unclear risk	No information is given.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigators were aware of the dosage group, but unaware of the substance infused (IVIG or placebo).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial was double-blind with investigators blinded to which treatment was received (IVIG or placebo) and the external outcome assessors (neurologists) also blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 patients in the treatment arm were excluded from the statistical evaluation of seizure frequency. 1 patient in the 100 mg/kg group dropped out (reasons unknown) 1 patient had continuous focal motor seizures (250 mg/kg group) 1 patient had unaccountable seizures after baseline (100 mg/kg) Excluded patients contributed to the best and worst-case scenario analyses.
Selective reporting (reporting bias)	Low risk	Protocol was unavailable but it appeared that all expected and pre-specified outcomes were reported.
Other bias	Unclear risk	None detected.

EEG: electroencephalogram; **IVIG**: intravenous immunoglobulin

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barbaro 2009	Study predominantly evaluating radiosurgery; some patients were given oral steroids where there was MRI evidence of oedema causing brain shift
Barile-Fabris 2005	Not specific to focal epilepsy and patients already had underlying immunological condition (SLE)
Klein 1970	Review of studies including various forms of epilepsy and not only focal epilepsy
Laxer 2000	Study of the neurosteroid ganaxolone which does not have any known immunomodulatory functions
Patel 2021	Different outcomes
Zhao 2021	Different outcomes

MRI: magnetic resonance imaging; **SLE**: systemic lupus erythematosus

Characteristics of studies awaiting classification *[ordered by study ID]*

Simko 1997

Methods	Effect of immunotherapy with transfer factor administered for a period of three months
Participants	Group of ten epileptic patients, treated with carbamazepine or primidone previously and throughout the study.
Interventions	Intravenous immunoglobulin
Outcomes	Out of eight patients, who finished the study we could notice significant reduction of epileptic discharges in eight patients.
Notes	-

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2021/02/030974

Study name	Trial of prednisolone (corticosteroid) in drug resistant epilepsy
Methods	Randomised, parallel group, placebo controlled trial
Participants	Males and females aged 18 to 50 years with uncontrolled epilepsy
Interventions	Corticosteroid
Outcomes	50% or more reduction in seizure frequency compared to baseline assessed at 12 weeks follow-up
Starting date	February 2021
Contact information	-

CTRI/2021/02/030974 *(Continued)*

Notes	-

NCT01545518

Study name	IVIG treatment for refractory immune-related adult epilepsy
Methods	Double-blind, cross-over study of IVIG treatment
Participants	Males and females aged 18 to 50 years with uncontrolled epilepsy
Interventions	Intravenous immunoglobulin
Outcomes	50% or greater decrease in seizure frequency two months following treatment with intravenous immunoglobulin
Starting date	November 2011
Contact information	-
Notes	-

DATA AND ANALYSES

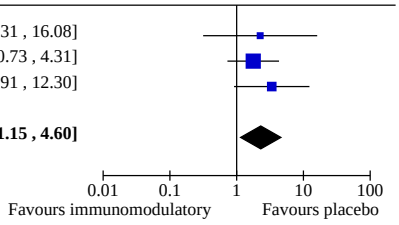
Comparison 1. Immunomodulatory interventions versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 50% responder	3	172	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [1.15, 4.60]
1.2 Treatment withdrawal	3	172	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.28, 3.80]
1.3 Any adverse effects	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.84, 1.59]

Analysis 1.1. Comparison 1: Immunomodulatory interventions versus placebo, Outcome 1: 50% responder

Study or Subgroup	Immunomodulatory therapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
French 2012	9	48	1	12	15.4%	2.25 [0.31 , 16.08]
French 2021	10	32	6	34	56.1%	1.77 [0.73 , 4.31]
Van Rijckevorsel-Harmant 1994	19	34	2	12	28.5%	3.35 [0.91 , 12.30]
Total (95% CI)		**114**		**58**	**100.0%**	**2.30 [1.15 , 4.60]**
Total events:	38		9			

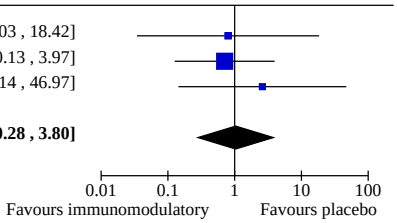
Heterogeneity: Chi² = 0.65, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.34 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Immunomodulatory interventions versus placebo, Outcome 2: Treatment withdrawal

Study or Subgroup	Immunomodulatory therapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
French 2012	1	48	0	12	17.8%	0.80 [0.03 , 18.42]
French 2021	2	32	3	34	65.7%	0.71 [0.13 , 3.97]
Van Rijckevorsel-Harmant 1994	3	34	0	12	16.5%	2.60 [0.14 , 46.97]
Total (95% CI)		**114**		**58**	**100.0%**	**1.04 [0.28 , 3.80]**
Total events:	6		3			

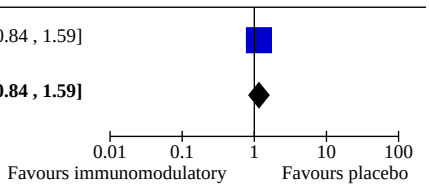
Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Immunomodulatory interventions versus placebo, Outcome 3: Any adverse effects

Study or Subgroup	Immunomodulatory therapy Events	Total	Palcebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
French 2021	24	32	22	34	100.0%	1.16 [0.84 , 1.59]
Total (95% CI)		**32**		**34**	**100.0%**	**1.16 [0.84 , 1.59]**
Total events:	24		22			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.91 (P = 0.36)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Immunomodulatory agents

Class	Drugs
Antimetabolites	• Antifolate drugs (Methotrexate) • Pyrimidine synthesis inhibitors (Leflunomide, Teriflunomide) • Urine synthesis inhibitors (Azathioprine, Mycophenolic acid)
Macrolides and other IL-2 inhibitors	Abetimus, Ciclosporin, Gusperimus, Pimecrolimus, Tacrolimus
TNF/TNFα inhibitors	Etanercept, Lenalidomide, Pegsunercept, Thalidomide
Caspase-1 inhibitors	VX-765
IL-1 receptor antagonist	Anakinra
Intravenous immunoglobulins	7-S native immunoglobulins
mTOR signalling pathway interference	Biolimus A9, Deforolimus, Everolimus, Sirolimus, Temsirolimus, Zotarolimus
Monoclonal antibodies	• BLyS (Belimumab) • CAT (Bertilimumab, Lerdelimumab, Metelimumab) • CD3 (Muromonab-CD3, Otelixizumab, Teplizumab, Visilizumab) • CD4 (Clenoliximab, Keliximab, Zanolimumab)

Table 1. Immunomodulatory agents *(Continued)*

	• CD11a (Efalizumab) • CD18 (Erlizumab) • CD20 (Afutuzumab, Ocrelizumab, Pascolizumab, Rituximab) • CD23 (Lumiliximab) • CD40 (Teneliximab, Toralizumab) • CD62 L/L-selectin (Aselizumab) • CD80 (Galiximab) • CD147/basigin (Gavilimomab) • CD154 (Ruplizumab) • Complement component 5 (Ecluzimab) • CTLA-4 (Ipilimumab, Tremelimumab) • IL-2 receptor/CD25 (Basiliximab, Daclizumab, Inolimomab) • IL-5 (Mepolizumab) • IL-6 (Elsilimomab) • IL-6 receptor (Tocilizumab) • IL-12 and IL-13 (Lebrikizumab, Ustekinumab) • Immunoglobulin E (Omalizumab) • Integrin (Natalizumab) • Interferon (Faralimomab) • Lymphocyte function-associated antigen (LFA)-1 (Odulimumab) • Miscellaneous (Atorolimumab, Cedelizumab, Dorlixizumab, Fontolizumab, Gantenerumab, Gomiliximab, Maslimomab, Morolimumab, Pexelizumab, Reslizumab, Rovelizumab, Siplizumab, Talizumab, Vapaliximab, Vepalimom • T-lymphocyte (Zolimomab Aritox) • TNFs (Adalimumab, Afelimomab, Certolizumab pegol, Golimumab, Infliximab)
Polyclonal antibodies	Anti-thymocyte globulin and anti-lymphocyte globulin

TNF: tumour necrosis factor

APPENDICES

Appendix 1. CRS Web search strategy

1. MESH DESCRIPTOR Epilepsies, focal EXPLODE ALL AND CENTRAL:TARGET

2. ((focal or focal) and (seizure* or epilep*)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

3. #1 OR #2 AND CENTRAL:TARGET

4. MeSH DESCRIPTOR Adrenal Cortex Hormones Explode All AND CENTRAL:TARGET

5. MeSH DESCRIPTOR Steroids Explode All AND CENTRAL:TARGET

6. MeSH DESCRIPTOR Prednisolone Explode All AND CENTRAL:TARGET

7. MeSH DESCRIPTOR Hydrocortisone Explode All AND CENTRAL:TARGET

8. MeSH DESCRIPTOR Methylprednisolone Explode All AND CENTRAL:TARGET

9. MeSH DESCRIPTOR Dexamethasone Explode All AND CENTRAL:TARGET

10. MeSH DESCRIPTOR Adrenocorticotropic Hormone Explode All AND CENTRAL:TARGET

11. MeSH DESCRIPTOR Immunosuppressive Agents Explode All AND CENTRAL:TARGET

12. MeSH DESCRIPTOR Adjuvants, Immunologic Explode All AND CENTRAL:TARGET

13. MeSH DESCRIPTOR Methotrexate Explode All AND CENTRAL:TARGET

14. MeSH DESCRIPTOR Azathioprine Explode All AND CENTRAL:TARGET

15. MeSH DESCRIPTOR Immunoglobulins Explode All AND CENTRAL:TARGET

16. MeSH DESCRIPTOR Cytokines Explode All AND CENTRAL:TARGET

17. MeSH DESCRIPTOR Caspase Inhibitors Explode All AND CENTRAL:TARGET

18. (glucocortico* or corticosteroid* or steroid* or prednisolone or hydrocortisone or dexamethasone or methylprednisolone or ACTH):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

19. ((adrenocorticotrophic next hormone) or (adrenocorticotropic next hormone)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

20. (immunosuppress* or immunomodulat* or immunoglobulin* or globulin*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

21. (abetimus or adalimumab or afelimomab or afutuzumab or anakinra or aselizumab or atorolimumab or azathioprine):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

22. (basiliximab or belimumab or bertilimumab or "biolimus A9" or cedelizumab or "certolizumab pegol" or ciclosporin or clenoliximab or cyclosporin*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

23. (daclizumab or deforolimus or dorlixizumab or ecluzimab or efalizumab or elsilimomab or erlizumab or etanercept or everolimus or faralimomab or fontolizumab or galiximab or gantenerumab or gavilimomab or golimumab or gomiliximab or gusperimus):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

24. (infliximab or inolimomab or ipilimumab or keliximab or lebrikizumab or leflunomide or lenalidomide or lerdelimumab or lumiliximab or maslimomab or mepolizumab or metelimumab or methotrexate or morolimumab or "muromonab-CD3" or "mycophenolic acid"):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

25. (natalizumab or ocrelizumab or odulimumab or omalizumab or otelixizumab or pascolizumab or pegsunercept or pexelizumab or pimecrolimus or reslizumab or rituximab or rovelizumab or ruplizumab):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

26. (siplizumab or sirolimus or tacrolimus or talizumab or temsirolimus or teneliximab or teplizumab or teriflunomide or thalidomide or tocilizumab or toralizumab or tremelimumab):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

27. (ustekinumab or vapaliximab or vepalimomab or visilizumab or zanolimumab or "zolimomab aritox" or zotarolimus):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

28. ((cytokine* or interleukin* or caspase*) ADJ3 (inhibit* or antagonis*)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

29. ("VX-765" or "VX765" or "VX 765"):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

30. #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 AND CENTRAL:TARGET

31. #3 AND #30 AND CENTRAL:TARGET

32. >22/08/2017:CRSCREATED AND CENTRAL:TARGET

33. #31 AND #32

Appendix 2. MEDLINE search strategy

This strategy includes a modification of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials published in Lefebvre 2021.

1. exp Adrenal Cortex Hormones/ or exp Steroids/ or exp Prednisolone/ or exp Hydrocortisone/ or exp Methylprednisolone/ or exp Dexamethasone/ or exp Adrenocorticotropic Hormone/ or exp Immunosuppressive Agents/ or exp Adjuvants, Immunologic/ or exp Methotrexate/ or exp Azathioprine/

2. (glucocortico$ or corticosteroid$ or steroid$ or prednisolone or hydrocortisone or dexamethasone or methylprednisolone or ACTH).mp.

3. (adrenocorticotrop?ic adj hormone).mp.

4. (immunosuppress$ or immunomodulat$ or immunoglobulin$ or abetimus or adalimumab or afelimomab or afutuzumab or anakinra or aselizumab or atorolimumab or azathioprine or basiliximab or belimumab or bertilimumab or biolimus A9 or cedelizumab or certolizumab pegol or ciclosporin or clenoliximab or cyclosporin$ or daclizumab or deforolimus or dorlixizumab or ecluzimab or efalizumab or elsilimomab or erlizumab or etanercept or everolimus or faralimomab or fontolizumab or galiximab or gantenerumab or gavilimomab or golimumab or gomiliximab or gusperimus or infliximab or inolimomab or ipilimumab or keliximab or lebrikizumab or leflunomide or lenalidomide or lerdelimumab or lumiliximab or maslimomab or mepolizumab or metelimumab or methotrexate or morolimumab or muromonab-CD3 or mycophenolic acid or natalizumab or ocrelizumab or odulimumab or omalizumab or otelixizumab or pascolizumab or pegsunercept or pexelizumab or pimecrolimus or reslizumab or rituximab or rovelizumab or ruplizumab or siplizumab or sirolimus or tacrolimus or talizumab or temsirolimus or teneliximab or teplizumab or teriflunomide or thalidomide or tocilizumab or toralizumab or tremelimumab or ustekinumab or vapaliximab or vepalimomab or visilizumab or zanolimumab or zolimomab aritox or zotarolimus).mp.

5. exp Immunoglobulins/ or globulin$.mp.

6. exp Cytokines/ or exp Caspase Inhibitors/

7. ((cytokine$ or interleukin$ or caspase$) adj3 (inhibit$ or antagonis$)).mp.

8. ("VX-765" or VX765 or "VX 765").mp.

9. or/1-8

10. exp Epilepsies, focal/

11. ((focal or focal) and (seizure$ or epilep$)).mp.

12. 10 or 11

13. exp controlled clinical trial/ or (randomi?ed or placebo or randomly).ab.

14. clinical trials as topic.sh.

15. trial.ti.

16. 13 or 14 or 15

17. exp animals/ not humans.sh.

18. 16 not 17

19. 9 and 12 and 18

20. limit 19 to ed=20170822-20211111

21. 19 not (1$ or 2$).ed.

22. 21 and (2017$ or 2018$ or 2019$ or 2020$ or 2021$).dt.

23. 20 or 22

24. remove duplicates from 23

WHAT'S NEW

Date	Event	Description
16 October 2023	New search has been performed	Searches updated 11 November 2021. Two new studies have been included.
16 October 2023	New citation required and conclusions have changed	Conclusions have changed.

HISTORY

Protocol first published: Issue 7, 2012
Review first published: Issue 6, 2013

CONTRIBUTIONS OF AUTHORS

LW was primarily responsible for the writing of this update and completing data extraction and risk of bias assessments.

MP assessed the studies for eligibility, extracted data and assessed risk of bias.

AGM provided guidance and manuscript feedback during the update process.

DECLARATIONS OF INTEREST

MP: none known.

LW: none known.

AGM: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Marson is funded in part by the NIHR Applied Research Collaboration, North West Coast (NIHR ARC NWC). Professor Marson is a National Institute for Health and Care Research (NIHR) Senior Investigator. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care. Professor Marson is the Co-ordinating Editor of the Cochrane Epilepsy Group; however, he was not involved in the editorial process of this review update.

SOURCES OF SUPPORT

Internal sources

- New Source of support, UK

  Cochrane Methodology Review Group

External sources

- National Institute for Health and Care Research (NIHR), UK

  This review update was funded by the National Institute for Health Research (NIHR)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The term "partial" has been replaced by "focal" in accordance with the most recent International League Against Epilepsy classification (Scheffer 2017).

For the current version of this review we have included children in the analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects]; *Drug Resistant Epilepsy [drug therapy]; Drug Therapy, Combination; *Drug-Related Side Effects and Adverse Reactions; *Epilepsies, Partial [chemically induced] [drug therapy]; Quality of Life; Randomized Controlled Trials as Topic; Seizures [drug therapy]

MeSH check words

Adult; Aged; Child; Humans