NHS England Evidence Review:

Tocilizumab for neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) refractory or intolerant to previous lines of therapy

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of tocilizumab compared with current standard of care or best supportive care, with or without corticosteroids, in people with neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) who are intolerant to, or whose disease is refractory to, previous lines of therapy.

NMOSD can be stratified by the serological presence or absence of aquaporin-4 water antibodies (AQP4-IgG): AQP4-IgG positive NMOSD or AQP4-IgG negative NMOSD. The disorders are commonly characterised by recurrent relapses of optic neuritis and longitudinally extensive transverse myelitis. MOGAD is associated with the presence of myelin oligodendrocyte glycoprotein (MOG) antibodies. The clinical phenotype of MOGAD differs but overlaps with that of NMOSD and includes acute disseminated encephalomyelitis, brainstem and cerebral cortical encephalitis, as well as optic neuritis and myelitis. All people with AQP4-IgG positive disease and around 45% of people with MOGAD have chronic relapsing disease. Monophasic AQP4-IgG negative disease and monophasic MOGAD are out of scope of this review.

Tocilizumab is a humanised monoclonal antibody that targets the interleukin-6 (IL-6) receptor. Studies have identified that IL-6, a proinflammatory cytokine, plays a pivotal role in the damage to the central nervous system and demyelination in AQP4-IgG positive NMOSD. Biomarker studies both during and between acute attacks demonstrate elevated levels of IL-6 in the serum and cerebrospinal fluid. Early immunohistochemical, histopathological and clinical evidence suggest that IL-6 may play a similar role in MOGAD.

Current standard of care is outlined in the NHS England service specification for NMOSD, for those who meet the diagnostic criteria. First line treatment for NMOSD and MOGAD is corticosteroids which can be given in combination with either azathioprine, mycophenolate or methotrexate. Rituximab is commissioned for people with either AQP4-IgG positive NMOSD, or those with MOGAD, or people with AQP4-IgG negative NMOSD that fulfils the 2015 International consensus diagnostic criteria for NMOSD, who are refractory to first line treatment. Immunoglobulin therapy has been approved by NHS England for people with NMOSD (both AQP4-IgG positive and negative) who have failed or are intolerant to at least 3 treatments and those with MOGAD who are refractory to at least 2 treatments. All commissioned treatments for NMOSD and MOGAD are off-label. None of the UK licensed treatments for NMOSD or MOGAD are marketed or available in the UK. All NICE technology appraisals for treating NMOSD have been discontinued or terminated, due to the manufacturers not providing, or withdrawing, evidence submissions (eculizumab, ravulizumab, satralizumab and inebilizumab).

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of tocilizumab compared with current standard of care or best supportive care, with or without corticosteroids, in people with neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) who are intolerant to, or whose disease is refractory to, previous lines of therapy. In addition, the review scope includes the identification of possible subgroups of people within the included studies who might benefit from tocilizumab more than the wider population of interest. It also includes what dose and route of administration of tocilizumab was used by the included studies and the criteria used to define NMOSD and MOGAD.

The searches for evidence published since January 2014 were conducted on 28 February 2024 and identified 493 references. The titles and abstracts were screened and 30 full text papers were obtained and assessed for relevance.

Three papers were identified for inclusion in the evidence review. One phase 2, open-label, randomised trial (Zhang et al. 2020) with 118 participants comparing tocilizumab to azathioprine, and 2 retrospective, observational, before and after studies (Ringelstein et al. 2022; Yang et al. 2023) including 57 and 65 participants, respectively. Ringelstein et al. 2022 was based across Europe (including the UK) and the US, and the other 2 studies were based in East Asia. The open-label randomised trial had a follow up period of up to 90 weeks. The observational studies had median durations of 23.8 and 34.1 months.

In terms of clinical effectiveness in people with NMOSD or MOGAD:

Critical outcomes

- Relapse rate.
  - One open-label randomised trial (Zhang et al. 2020) and 2 retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided very low and moderate certainty evidence that tocilizumab reduces relapse rate up to a median treatment duration of 34.1 months. Moderate certainty evidence from the open-label randomised trial showed that relapse rate was statistically significantly reduced with tocilizumab compared with azathioprine at up to 90 weeks (hazard ratio [HR]) 0.236; p<0.0001). Very low certainty evidence from the 2 retrospective observational studies showed statistically significant reductions in median annualised relapse rate (ARR) with tocilizumab: from 1.5 before treatment to 0 after 23.8 months (p<0.001) and from 1.9 before treatment to 0.1 after 34.1 months (p<0.0001). Across all 3 studies, the time to first relapse on tocilizumab was between 9 months and 78.9 weeks (about 18 months). Moderate certainty evidence showed that compared with azathioprine, time to first relapse was statistically significantly longer in the tocilizumab group (p=0.0026).
- Measure of disability.
  - The Expanded Disability Status Scale (EDSS) score. One open-label randomised trial (Zhang et al. 2020) provided moderate certainty evidence that tocilizumab reduced disability progression at up to 24 weeks compared with azathioprine; this was statistically significant at 12 weeks (p=0.0087). The same study provided moderate certainty evidence that statistically significantly more participants in the azathioprine group than in the tocilizumab group experienced a worsening EDSS score at up to 90 weeks (relative risk [RR] 3.667; p=0.0005). Very low certainty evidence from 2 retrospective observational studies (Ringelstein et al. 2022; Yang et

al. 2023) showed that 8% and 9% of participants taking tocilizumab had a worsening EDSS score up to a median treatment duration of 34.1 months. Moderate certainty evidence from the open-label randomised trial showed that those taking tocilizumab had an improvement in mean EDSS score of 0.32 at up to 90 weeks, but there was no difference between the tocilizumab and azathioprine groups (p=0.242). Very low certainty evidence from 1 retrospective observational study (Ringelstein et al. 2022) showed a reduction in median EDSS score of 1.0 after 23.8 months of tocilizumab treatment but no statistical analyses were reported.
  - Visual acuity. One open-label randomised trial (Zhang et al. 2020) provided very low to moderate certainty evidence that tocilizumab did not have a beneficial impact on LogMAR, high-contrast or low-contrast visual acuity at 60 weeks, compared with azathioprine. However, moderate certainty evidence from the same trial showed a statistically significantly lower risk of optic neuritis with tocilizumab compared with azathioprine (HR 0.182; p=0.011).
- Symptom alleviation.
  - Two retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided very low certainty evidence that tocilizumab did not improve chronic pain up to a median treatment duration of 34.1 months, but no statistical analyses were reported. No comparator was available for this outcome.

Important outcomes

No evidence was identified for the following outcomes:

- Health related quality of life.
- Hospitalisations / hospital appointments.
- Corticosteroid reduction.

In terms of safety in people with NMOSD or MOGAD:

- Frequency / number of adverse events.
  - One open-label randomised trial (Zhang et al. 2020) provided moderate certainty evidence that the incidence of adverse events, which were mostly mild, was similar in the tocilizumab (97%) and azathioprine (95%) groups. Severe and life-threatening adverse events were higher in the azathioprine (36%) than in the tocilizumab (15%) group. Two retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided very low certainty evidence on selected adverse events. All 3 studies reported similar adverse events, including raised liver enzyme levels, upper respiratory tract and urinary infections, and infusion-related reactions. None of the studies reported any statistical analyses.
- Discontinuation of treatment due to adverse events.
  - Moderate certainty evidence from 1 open-label randomised trial (Zhang et al. 2020) and very low certainty evidence from 1 retrospective observational study (Ringelstein et al. 2022) showed that adverse events leading to discontinuation of tocilizumab occurred in 2% and 9% of participants, respectively. In the open-label randomised trial, this was similar to those who discontinued azathioprine due to adverse events (3%). Neither study reported any statistical analyses.
- Mortality.
  - Moderate certainty evidence from 1 open-label randomised trial (Zhang et al. 2020) and very low certainty evidence from 1 retrospective observational study (Ringelstein

et al. 2022) suggested that tocilizumab does not have an impact on mortality, but the studies may be too small or too short to detect rare events. Neither study reported any statistical analyses.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of prespecified subgroups:

***In people with AQP4-IgG positive NMOSD*:**

- Relapse rate.
  - One open-label randomised trial (Zhang et al. 2020) provided evidence that showed that in participants with AQP4-IgG positive NMOSD (n=103) relapse rate was statistically significantly reduced with tocilizumab compared with azathioprine at up to 90 weeks (HR 0.202; p=0.0004). Two retrospective observational studies (Ringelstein et al. 2022, n=36; Yang et al. 2023, n=54) provided evidence that median ARR was reduced on tocilizumab treatment, compared with before treatment, up to a median treatment duration of 34.1 months (from 1.5 to 0; p<0.001 and from 1.89 to 0.14; p<0.0001), but the ranges indicate high variability in the results. The 2 retrospective observational studies also reported that time to relapse on tocilizumab was between 4.4 and 18.6 months, and between 56% and 76% of participants remained relapse free up to a median treatment duration of 34.1 months.
- Measure of disability.
  - Two retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided evidence that there were statistically significant reductions in median EDSS score compared with before tocilizumab treatment, up to a median duration of 34.1 months (from 6.25 to 4.25; p<0.003 and from 5.75 to 3.5; p<0.001 respectively), but the ranges indicate high variability in the results. Both studies also reported that about 8% of participants experienced a worsening EDSS score from baseline. No comparator was available for this outcome.
- Safety.
  - One retrospective observational study (Ringelstein et al. 2022) provided evidence that the safety profile of tocilizumab in participants with AQP4-IgG positive NMOSD is comparable to that in the wider study population. No comparator was available for this outcome.

In people with AQP4-IgG negative NMOSD:

- Relapse rate.
  - One open-label randomised trial (Zhang et al. 2020) provided evidence that there was no difference in the risk of relapse in participants with AQP4-IgG negative NMOSD (n=15) between tocilizumab and azathioprine at up to 90 weeks (HR 0.470; p=0.408). Two retrospective observational studies (Ringelstein et al. 2022, n=7; Yang et al. 2023, n=11) provided evidence that participants with AQP4-IgG negative NMOSD experienced statistically significant reductions in median ARR with tocilizumab, compared with before treatment, up to a median treatment duration of 34.1 months (from 3.0 to 0.2; p<0.032 and from 1.75 to 0.06; p<0.0001). The 2 retrospective observational studies also reported that the time to relapse on

tocilizumab was between 12.2 and 15.5 months, and between 43% and 82% of participants remained relapse free up to a median treatment duration of 34.1 months. The number of participants may be too small to draw definitive conclusions.

- Measure of disability.
  - Two retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided evidence which showed inconsistent results on the outcome of disability measured by change in EDSS scores. This may be due to low participant numbers. Both studies reported between 9% and 29% of participants receiving tocilizumab experienced a worsening EDSS score from baseline, up to a median treatment duration of 34.1 months. No comparator was available for this outcome.
- Safety.
  - One retrospective observational study (Ringelstein et al. 2022) provided evidence that the safety profile of tocilizumab in participants with AQP4-IgG negative NMOSD is comparable to that in the wider study population. No comparator was available for this outcome.

In people with MOGAD:

- Relapse rate.
  - One open-label randomised trial (Zhang et al. 2020) provided evidence for relapse rate in participants with MOGAD but numbers were small (n=3) so no statistical analyses were reported and it is difficult to draw conclusions. One retrospective observational study (Ringelstein et al. 2022, n=14) provided evidence that participants with MOGAD experienced a statistically significant reduction in median ARR with tocilizumab, compared with before treatment, up to a median treatment duration of 16.3 months (from 1.75 to 0; $p<0.0011$). The retrospective observational study also reported a time to relapse on tocilizumab of 9.4 months, and that 79% of participants remained relapse free up to a median treatment duration of 16.3 months.
- Measure of disability.
  - One retrospective observational study (Ringelstein et al. 2022) provided evidence which showed a statistically significant reduction in median EDSS score with tocilizumab from 2.75 at start of treatment to 2.0 ($p<0.031$), up to a median treatment duration of 16.3 months. It also reported that none of the participants with MOGAD experienced a worsening EDSS score. The number of participants may be too small to draw conclusions. No comparator was available for this outcome.
- Safety.
  - One retrospective observational study (Ringelstein et al. 2022) provided evidence that the safety profile of tocilizumab in participants with MOGAD is comparable to that in the wider study population. No comparator was available for this outcome.

When comparing outcomes in people with AQP4-IgG positive NMOSD and AQP4-IgG negative NMOSD:

- Evidence from 1 retrospective observational study (Ringelstein et al. 2022) showed no difference in relapse rate between participants with AQP4-IgG positive and negative NMOSD on tocilizumab. However, evidence from another retrospective observational study (Yang et al. 2023) showed that relapse counts on tocilizumab in those with AQP4-IgG negative NMOSD were, on average, 2.6 times those with AQP4-IgG positive NMOSD ($p<0.03$).

When comparing outcomes in people with MOGAD and AQP4-IgG positive NMOSD:

- Evidence from 1 retrospective observational study (Ringelstein et al. 2022) showed no difference in relapse rate on tocilizumab between those with MOGAD and those with AQP4-IgG positive NMOSD (p=0.86).

In terms of additional subgroups:

- One retrospective observational study (Yang et al. 2023) showed that in participants with NMOSD or MOGAD, taking tocilizumab with concomitant corticosteroids statistically significantly decreased ARR compared with tocilizumab monotherapy (p=0.0005). It also reported 81% of participants taking concomitant corticosteroids were relapse free, compared with 33% of those taking tocilizumab monotherapy. However, another retrospective observational study (Ringelstein et al. 2022) provided evidence that when corticosteroids were grouped with other immunosuppressants, 78% of those taking tocilizumab monotherapy were relapse free, compared with 40% of those taking it with concomitant immunosuppressants. This paper did not report any statistical analyses.
- One retrospective observational study (Yang et al. 2023) showed that in participants with NMOSD, receiving intravenous (IV) tocilizumab statistically significantly decreased median ARR compared with before treatment, regardless of the interval between infusions (4, 6 or 8 weeks). However, a logistic regression analysis showed that infusion intervals of greater than 4 weeks may increase relapse risk (OR 10.7; 95% CI 1.6 to 71.4; p=0.014).
- One open-label randomised trial (Zhang et al. 2020) and 1 retrospective observational study (Yang et al. 2023) both provided evidence that presence of concomitant autoimmune disease did not affect risk of relapse, in people with NMOSD or MOGAD on tocilizumab.

In terms of dose and route of administration of tocilizumab used in the studies:

- In Ringelstein et al. 2022, IV tocilizumab was administered at a mean interval of 31.6 (range 26.1 to 44.2) days, at a median dose of 8.0 (range 6.0 to 12.0) mg/kg. One participant received subcutaneous (SC) tocilizumab as weekly injections of 162 mg. In Yang et al. 2023, IV tocilizumab 8 mg/kg was administered at a mean interval of 37.5 (range 27 to 61) days. Infusions were given at intervals of 4, 6 or 8 weeks. In Zhang et al. 2020, IV tocilizumab 8 mg/kg was administered every 4 weeks.

In terms of how NMOSD or MOGAD was defined in the studies:

- In both Yang et al. 2023 and Zhang et al. 2020, eligibility criteria included meeting the 2015 international consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Ringelstein et al. 2022 did not provide details on their diagnostic eligibility criteria. However, they reported that 63% of participants fulfilled the 2006 diagnostic criteria for neuromyelitis optica. All participants with AQP4-IgG positive and negative NMSOD and 50% of participants with MOGAD also fulfilled the 2015 international consensus diagnostic criteria for neuromyelitis optica spectrum disorders.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

Quality assessment of Zhang et al. 2020 found a low risk of bias in most domains, but participants and treating physicians were not blinded.

Quality assessment of the observational non-comparative studies (Ringelstein et al. 2022; Yang et al. 2023) was rated poor, due to lack of blinding, unclear plans regarding statistical analyses, inconsistency in reporting statistical analyses, inaccuracies in reporting of data and uncertainty around use of validated tools. Any changes from before to after treatment could also be a result of regression to the mean, especially if tocilizumab was administered soon after a relapse.

Baseline characteristics of included studies generally seem well matched, although there were differences in baseline EDSS scores. Participants in Yang et al. 2023 had higher baseline EDSS scores and a wider range than the other studies. This could represent a broader population, both with milder and more severe disease than the other studies.

All included studies were downgraded for indirectness due to concerns around whether the included populations are applicable to the proposed population in UK clinical practice. Two of the studies (Yang et al. 2023 and Zhang et al. 2020), had exclusion criteria regarding recent use of other immunosuppressants, and Zhang et al. 2020 also excluded people who had previously relapsed on azathioprine. This may exclude some of the relevant population, that is, those who are refractory to previous lines of therapy. Ringelstein excluded people with acute disseminated encephalomyelitis, which is a recognised clinical manifestation in people with MOGAD. There is also some uncertainty around the relapsing history, with participants in Ringelstein et al. 2022 and Yang et al. 2023 both reporting baseline characteristics which imply some participants had not experienced many, or any, relapses in the pre-study period.

Different administration regimens of tocilizumab were used across the studies. This included different treatment intervals, whether tocilizumab was used alone or with concomitant medication, what concomitant medication was allowed and how tocilizumab was administered (IV or SC). Outcomes are not always reported in sufficient detail to be able to determine the impact of these differences. Additionally, some participants in Yang et al. 2023 were taking concomitant prednisone, which is not licensed in the UK.

It is unclear where in the clinical pathway tocilizumab is being used. It is possible it is being positioned differently in each study and it is unclear how this relates to the proposed use of tocilizumab in UK clinical practice. While most participants are described as highly relapsing or were switched due to disease breakthrough or intolerance of previous immunosuppressants, none of the studies provide information regarding the number of treatments to which participants' disease was refractory or to which participants were intolerant.

Participant numbers were relatively small. This is particularly apparent for the subgroups, which makes drawing conclusions difficult. There were only 3 participants under the age of 18 years in Ringelstein et al. 2022, so no conclusions can be made in this population. There is also some uncertainty around identifying people with MOGAD: it is unclear if participants were systematically screened for MOGAD and it is possible that the reported AQP4-IgG negative populations may have included some participants with unidentified MOGAD.

Zhang et al. 2020 used a different definition for relapse than Ringelstein et al. 2022 and Yang et al. 2023. The difference in definition could impact the number of relapses detected in the study, but it is uncertain whether more or less would be detected.

All studies used the Expanded Disability Status Scale (EDSS) to measure disability, a scale developed for use in multiple sclerosis. While EDSS is used widely in clinical practice in

NMOSD and MOGAD, it has not been the subject of a validation study in these populations. The European Medicines Agency (EMA) guidance on the clinical investigation of medicinal products for the treatment of multiple sclerosis warn against using change in EDSS score from baseline as a measure of efficacy in multiple sclerosis. However, a relapse in people with NMOSD or MOGAD may cause more significant disability than a relapse in people with multiple sclerosis. Therefore, change in EDSS score from baseline, reported by both Zhang et al. 2020 and Ringelstein et al. 2022, may be a more meaningful measure in NMOSD and MOGAD. However, in the absence of a validation study, there is uncertainty as to the amount of clinically meaningful change seen. Zhang et al. 2020 reported disability progression, based on the EDSS, which is considered to be an appropriate measure of efficacy in the EMA guidance. While time to relapse and ARR are reported to be appropriate measures by the EMA, Yang et al. 2023 does not report their method for calculating ARR, which makes comparisons difficult.

Conclusion

Results from 1 open-label randomised trial, which compared tocilizumab with azathioprine, and results from 2 retrospective, before and after, observational studies, provide very low and moderate certainty evidence to suggest that relapse rate is reduced by tocilizumab in people with NMOSD or MOGAD. This benefit was also seen in participants with AQP4-IgG positive NMOSD, though there is more variation in these results. It is difficult to draw conclusions in the MOGAD and AQP4-IgG negative NMOSD populations, due to the small number of participants.

In terms of disability measured using EDSS, Zhang et al. 2020 provides moderate certainty evidence and Ringelstein et al. 2022 and Yang et al. 2023 provide very low certainty evidence that disability progression may be limited by tocilizumab in people with NMOSD or MOGAD. It is more difficult to draw conclusions on the subgroups. Some reductions in EDSS scores were seen but they may not be clinically meaningful and some of the results had high variability. However, limiting disease progression, rather than improving disability, is likely to be the main target of therapy.

Very low to moderate certainty evidence suggests that there is no difference in visual acuity with tocilizumab compared with azathioprine (Zhang et al. 2020). However, a statistically significant reduction in optic neuritis attacks was seen in the tocilizumab group compared with the azathioprine group, which may be impactful for individuals.

Very low certainty evidence in the retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) showed that tocilizumab did not moderate pain in participants with NMOSD or MOGAD.

Very low to moderate certainty evidence showed that the safety profile of tocilizumab, when used in people with NMOSD or MOGAD, is similar to that reported for other autoimmune conditions (tocilizumab summary of product characteristics).

The 2 retrospective observational studies provide some evidence on direct comparisons between subgroups. They provide limited evidence to suggest there is no difference in relapse rate between participants with MOGAD and participants with AQP4-IgG positive NMOSD when treated with tocilizumab. However, the evidence on comparisons between positive and negative AQP4-IgG NMOSD is inconsistent, so no conclusions can be drawn.

Limited evidence shows that concomitant corticosteroids may decrease risk of relapse and giving IV tocilizumab at intervals greater than 4 weeks may increase risk of relapse (Yang et al. 2023). The same study and Zhang et al. 2020 provide evidence to show that having a concomitant autoimmune disease does not affect relapse rate in participants being treated with tocilizumab.

No evidence was found:

- for people under 18 years.
- for the important outcomes of health related quality of life, hospitalisation or hospital appointments, or corticosteroid reduction.
- to determine whether tocilizumab is a cost-effective treatment for people with NMOSD or MOGAD.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In patients with neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) who are intolerant to or whose disease is refractory to previous lines of therapy, what is the clinical effectiveness of tocilizumab compared with current standard of care or best supportive care?
2. In patients with NMOSD or MOGAD who are intolerant to or whose disease is refractory to previous lines of therapy, what is the safety of tocilizumab compared with current standard of care or best supportive care?
3. In patients with NMOSD or MOGAD who are intolerant to or whose disease is refractory to previous lines of therapy, what is the cost effectiveness of tocilizumab compared with current standard of care or best supportive care?
4. From the evidence selected, are there any subgroups of patients that may benefit from tocilizumab more than the wider population of interest?
5. From the evidence selected, what dose and route of administration of tocilizumab was used?
6. From the evidence selected, how was NMOSD or MOGAD defined?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 28 February 2024.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Three papers were identified for inclusion (Ringelstein et al. 2022, Yang et al. 2023 and Zhang et al. 2020). Table 1 provides a summary of these included studies and full details are given in Appendix E. One was a phase 2, multicentre, open-label, randomised trial (Zhang et al. 2020), and 2 were retrospective, before and after, observational studies (Ringelstein et al. 2022; Yang et al. 2023).

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Ringelstein et al. 2022 Retrospective, before and after, observational study Europe (including UK) and USA	People with relapsing MOGAD, classical AQP4-IgG positive NMOSD or double-seronegative NMOSD. • N=57. • Mean (standard deviation [SD]) age at start of tocilizumab treatment 42.2 (±14.3) years; 3 were under 18 years. • 44 (77%) female, 13 (23%) male. • 14 (25%) MOGAD, 36 (63%) AQP4-IgG positive NMOSD, 7 (12%) double-seronegative NMOSD. • All had been treated with immunotherapies prior to tocilizumab treatment and all had received rituximab. • 45/57 (79%) switched to tocilizumab due to ongoing disease activity, 5/57 (9%) due to side effects of prior immunotherapies, 6/57 (10%) because of concomitant disease activity and adverse events, 1/57 (2%) had neutralising antibodies against rituximab. • 50/57 fulfilled NMOSD 2015 criteria (36/36 with AQP4-IgG positive NMOSD, 7/7 with double-seronegative NMOSD, 7/14 with MOGAD); 36/57 fulfilled NMOSD 2006 criteria (27/36 with AQP4 positive NMOSD, 5/7 with double-seronegative NMOSD, 4/14 with MOGAD).	**Intervention** IV tocilizumab in 56 participants; mean interval of 31.6 days (range 26.1 to 44.2 days); median dose of 8.0 mg/kg (range 6.0 to 12.0 mg/kg). SC tocilizumab in 1 participant; weekly doses of 162 mg. Median treatment duration 23.8 months (IQR 13.0 to 51.1 months). Thirteen participants had a treatment duration of less than 1 year (median 0.5 years). The mean (SD) number of tocilizumab infusions given was 34.0 (±28.2). Tocilizumab was given as add-on therapy in 20/57 (35%), this was due to comorbidities in 2/20 (10%). **Comparison** No comparator.	**Critical outcomes** • Change in median ARR between baseline and after a median treatment duration of 23.8 (primary outcome). • Median time to first relapse. • Percentage relapse free after a median treatment duration of 23.8 months. • Change in median EDSS scores between baseline and after a median treatment duration of 23.8 months. • Worsening of EDSS score after a median treatment duration of 23.8 months. • Change in median chronic pain occurrence and intensity scores between baseline and at last follow up during a median treatment duration of 23.8 months. **Important outcomes** • Safety during a median treatment duration of 23.8 months (AEs leading to discontinuations; incidence of selected AEs; mortality).
Yang et al. 2023 Retrospective, before and after, observational study China	Adults (aged ≥18 years), diagnosed with NMOSD based on the 2015 international consensus diagnostic criteria, who received tocilizumab. • N=65. • 92% female; mean (SD) age at tocilizumab initiation 48.3 (±14.5) years. • n=54 (83%) AQP4-IgG positive NMOSD, n=11 (17%) AQP4-IgG negative NMOSD (people with MOGAD were excluded). • All had received corticosteroids prior to tocilizumab treatment. Other agents used prior to tocilizumab treatment were IVIG (35/65, 53.8%), mycophenolate (17/65, 26.1%), azathioprine (15/65, 23.1%), rituximab (12/65, 18.5%) and cyclophosphamide (1/65, 1.5%). • Participants had switched to tocilizumab mainly due to disease breakthrough or adverse events under prior immunosuppressants (figures not reported).	**Interventions** IV tocilizumab 8 mg/kg; mean interval of 37.5 days (range 27 to 61 days). Planned infusion intervals were 4, 6 and 8 weeks. All participants discontinued prior immunosuppressants, except oral corticosteroids, at tocilizumab initiation. 59/65 (90.8%) were taking oral prednisone at a median dose of 25 mg (range 15 to 40 mg) when tocilizumab was started – these were gradually tapered and discontinued within a median of 4.2 months (range 3 to 8 months), at which point tocilizumab was used as monotherapy. All prior treatments were discontinued in 6/65 (9.2%) participants and tocilizumab was used as monotherapy from the start. Median follow up 34.1 months (IQR 25.5 to 39.3 months). **Comparators** No comparator.	**Critical outcomes** • Change in median ARR between baseline and after a median treatment duration of 34.1 months (primary outcome). • Median time to first relapse. • Percentage relapse free after a median treatment duration of 34.1 months. • Worsening of EDSS score after a median treatment duration of 34.1 months. • Change in median NMOSD-related pain intensity score between baseline and after a median treatment duration of 34.1 months. **Important outcomes** • Safety during a median treatment duration of 34.1 months (incidence of selected AEs).

Zhang et al. 2020 Open-label, multicentre, randomised phase 2 trial China	Adults (≥18 years) with highly relapsing NMOSD who were diagnosed according to 2015 international consensus diagnostic criteria, had an EDSS score of 7.5 or lower, and a history of at least 2 clinical relapses during the previous 12 months, or 3 relapses in the previous 24 months, with at least 1 relapse in the previous 12 months. • N=118. • n=59 tocilizumab, n=59 azathioprine. • 91.5% female; mean (SD) age was 48.1 (±13.4) and 45.3 (±14.5) years in the tocilizumab and azathioprine groups, respectively. • 50 (85%) of the tocilizumab and 53 (90%) of the azathioprine participants were AQP4-IgG positive. Three participants in the AQP4-IgG negative group had MOGAD – 1 participant on the tocilizumab group and 2 in the azathioprine group. • Immunosuppressant therapy at baseline was similar with 39% in both the tocilizumab and azathioprine groups being treated with monotherapy and 57% and 61% in the azathioprine and tocilizumab groups being on dual therapy. An additional 1 participant was on intravenous immunoglobulin monotherapy, and 1 other was on no treatment, both in the tocilizumab group.	**Intervention** IV tocilizumab (8 mg/kg every 4 weeks). For infusion related reactions, infusion rate changes and prednisone or diphenhydramine were permitted. Concomitant immunosuppressants were permitted for the first 12 weeks, thereafter tocilizumab was used as monotherapy. **Comparison** Oral azathioprine, initially 25 mg, increased stepwise in 25 mg per day increments until a target dose of 2 to 3 mg/kg per day was reached. For medication related side effects during the loading period, symptomatic treatments were allowed (apart from new immunosuppressants). Concomitant immunosuppressants were permitted for those randomised to azathioprine during the first 24 weeks: • those without previous azathioprine treatment received 24 weeks of concomitant treatment • those who had less than 24 weeks of azathioprine treatment previously received concomitant immunosuppressants until they had received 24 weeks of azathioprine treatment • those who had previously had azathioprine for longer than 24 weeks received no concomitant immunosuppressants. After 24 weeks, azathioprine was used as monotherapy. The study had a minimum follow up period of 60 weeks, with a stopping criterion of at least 30 relapses. Participants reached the end of the study they relapsed, or when the last enrolled participant completed their last scheduled visit. Some participants (68/118, 58%) were followed up for 90 weeks due to length of time required to recruit the sample size.	**Critical outcomes** • Median time to first relapse (primary outcome). • Risk of relapse at 60 and 90 weeks. • Percentage relapse free during the 60 or 90 week follow up period. • Confirmed disability progression at 12 weeks. • Confirmed disability progression at 24 weeks (exploratory outcome). • Worsening of EDSS score between baseline and at end of the 60 or 90 week follow up. • Mean change in EDSS score between baseline and at end of the 60 or 90 weeks follow up. • Risk of optic neuritis (no follow up time reported). • Mean difference in LogMAR visual acuity between baseline and 60 weeks. • Mean difference in high-contrast letter score between baseline and 60 weeks (exploratory outcome). • Mean difference in low-contrast letter score between baseline and 60 weeks (exploratory outcome). **Important outcomes** • Safety during the 60 or 90 week follow up period (incidence of AEs; AEs leading to discontinuation; SAEs; severe and life-threatening AEs; mortality).

Abbreviations

AE, adverse event; ARR, annualised relapse rate; AQP4-IgG, aquaporin-4 immunoglobulin G; EDSS, Expanded Disability Status Scale; IQR, interquartile range; IVIG, intravenous immunoglobulin; IV, intravenous; LogMAR, Logarithm of the Minimum Angle of Resolution; mg/kg, milligrams per kilogram; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation.

5. Results

In patients with neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) who are intolerant to, or whose disease is refractory to, previous lines of therapy, what is the clinical effectiveness and safety of tocilizumab compared with current standard of care or best supportive care?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Relapse rate in people with NMOSD or MOGAD **Certainty of evidence:** Very low and moderate	This outcome is important to patients because relapse rates contribute to disability progression and may be associated with a significant reduction in quality of life. One open-label randomised trial (Zhang et al. 2020) and 2 retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided evidence relating to relapse rate. In the Zhang et al. 2020 open-label randomised trial (n=118), participants were adults (≥18 years) with highly relapsing NMOSD diagnosed according to 2015 international consensus diagnostic criteria for NMOSD. One hundred and three (87%) participants were AQP4-IgG positive, 15 (13%) were AQP4-IgG negative and of these 15, 3 (3%) were MOG positive. The planned follow up period for this study was 60 weeks, although some participants were followed up for 90 weeks, due to the time taken to recruit the required sample size. In the Yang et al. 2023 retrospective, before and after, observational study (n=65) participants were adults (≥18 years) diagnosed with NMOSD according to 2015 international consensus diagnostic criteria for NMOSD. Fifty-four (83%) participants were AQP4-IgG positive and 11 (17%) were AQP4-IgG negative; people with MOGAD were excluded. The median treatment duration was 34.1 (IQR 25.5 to 39.3) months. In the Ringelstein et al. 2022 retrospective, before and after, observational study (n=57), 3 participants were under 18 years old when switching to tocilizumab, the rest were adults (≥18 years). Thirty-six (63%) were AQP4-IgG positive, 14 (25%) were MOG positive and 7 (12%) were negative for both AQP4-IgG and MOG antibodies (referred to as double-seronegative in the paper and classified as AQP4-IgG negative in this section). The median treatment duration was 23.8 (IQR 13.0 to 51.1) months. **Risk of relapse** At 60 weeks: • One open-label randomised trial (Zhang et al. 2020) showed that risk of relapse was statistically significantly lower in the tocilizumab group compared with the azathioprine group (HR 0.274, 95% CI 0.123 to 0.607; p=0.0006). **(MODERATE)** At up to 90 weeks: • One open-label randomised trial (Zhang et al. 2020) showed a statistically significant reduction in the number of participants who experienced a relapse in the tocilizumab group (8/59, 14%) compared with the azathioprine group (28/59, 47%) (HR 0.236, 95% CI 0.107 to 0.518; p<0.0001). **(MODERATE)** **Percentage relapse free** At up to 90 weeks:

	• In a per protocol analysis, 1 open-label randomised trial (Zhang et al. 2020) (n=108) showed a statistically significant increase in the proportion of participants who were relapse free in the tocilizumab group (50/56, 89%) compared with the azathioprine group (29/52, 56%) (HR 0.188, 95% CI 0.076 to 0.463; p<0.0001). **(MODERATE)** The per protocol analysis included all participants who used tocilizumab or azathioprine as monotherapy. After a median treatment duration of 23.8 (IQR 13.0 to 51.1) months: • One retrospective observational study (Ringelstein et al. 2022) showed that 34/57 (60%) participants receiving tocilizumab were relapse free. **(VERY LOW)** After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: • One retrospective observational study (Yang et al. 2023) showed that 50/65 (76.9%) participants receiving tocilizumab were relapse free. Twenty relapses (14 myelitis and 6 optic neuritis cases) were reported by 15 participants. **(VERY LOW)** **Time to relapse** • One open-label randomised trial (Zhang et al. 2020) showed that the median time to first relapse was statistically significantly longer in the tocilizumab group (78.9 [IQR 58.3 to 90.6] weeks) than in the azathioprine group (56.7 [IQR 32.9 to 81.7] weeks) (p=0.0026) (primary outcome). **(MODERATE)** • One retrospective observational study (Ringelstein et al. 2022) showed that the median time to first relapse on tocilizumab was 9 months (range 0.5 to 47 months). **(VERY LOW)** • One retrospective observational study (Yang et al. 2023) showed that the median time to first relapse on tocilizumab was 15.5 months (range 4 to 42 months). **(VERY LOW)** **Annualised relapse rate (ARR)** After a median treatment duration of 23.8 (IQR 13.0 to 51.1) months: • One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median ARR (0) compared with the 2-year baseline period prior to tocilizumab treatment (1.5) (p<0.001, 95% CI 1.1 to 1.8) (primary outcome). (**VERY LOW)** After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: • One retrospective observational study (Yang et al. 2023) showed a statistically significantly reduction in median ARR (0.1, range 0 to 1.4) compared with before tocilizumab was started (1.9, range 0.1 to 6.3) (primary outcome) (p<0.0001, 95% CI 1.4 to 2.1). **(VERY LOW)** **One open-label randomised trial and 2 retrospective observational studies provided very low and moderate certainty evidence that tocilizumab reduces relapse rate up to a median treatment duration of about 34 months.** **Moderate certainty evidence from 1 open-label randomised trial showed that relapse rate was statistically significantly reduced, and time to first relapse was statistically significantly longer, with tocilizumab compared with azathioprine at up to 90 weeks. Very low certainty evidence from 2 retrospective observational studies showed statistically significant reductions in median ARR up to a median treatment duration of about 34 months. Although the clinical significance of the reductions in ARR are uncertain, the median ARR after tocilizumab treatment in the 2 observational**

	studies, was (or was close to) 0, indicating a paucity of relapses during the study periods.
Measure of disability in people with NMOSD or MOGAD: EDSS score **Certainty of evidence:** Very low to moderate	This outcome is important to patients because a measure of disability progression will likely be associated with a significant reduction in quality of life. One open-label randomised trial (Zhang et al. 2020) and 2 retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided evidence for disability. The follow up period varied by study from up to 90 weeks for the randomised trial, to a follow up after a tocilizumab median treatment duration of 23.8 (IQR 13.0 to 51.1) months in the Ringelstein et al. 2022 study and 34.1 (IQR 25.5 to 39.3) months in the Yang et al. 2023 study. **Expanded Disability Status Scale (EDSS)** The EDSS is a method of assessing an individual's level of disability and was developed for use in multiple sclerosis. It ranges from 0 (a normal neurological exam) to 10 (death due to multiple sclerosis). Increasing score represents a higher level of disability. A score up to 5 represents normal walking ability with some functional system impairment. A score above 5 represents impairment in mobility. **Disability progression** In Zhang et al. 2020, disability progression was defined as an increase in EDSS score of at least 1.0 point from baseline that was sustained on subsequent visits for at least 12 or 24 weeks if the baseline EDSS score was 5.5 or less. If the baseline EDSS score was greater than 5.5, disability progression was defined as an increase in the EDSS score of at least 0.5 points that was sustained for 12 or 24 weeks. At 12 weeks: • One open-label randomised trial (Zhang et al. 2020) showed that the number of participants with confirmed disability progression was statistically significantly lower in the tocilizumab group (5/59, 8%) compared with the azathioprine group (15/59, 25%) (HR 0.288, 95% CI 0.105 to 0.795, p=0.0087). **(MODERATE)** At 24 weeks: • One open-label randomised trial (Zhang et al. 2020) showed that the number of participants with confirmed disability progression was lower in the tocilizumab group (2/59, 3%) compared with the azathioprine group (6/59, 10%) (HR 0.221, 95% CI 0.047 to 1.042, p=0.0309) (exploratory outcome). **(LOW)** **Change in EDSS score** At up to 90 weeks: • One open-label randomised trial (Zhang et al. 2020) showed that there was no difference in the mean change in EDSS score in the tocilizumab group (−0.32, SD ±0.72) compared with the azathioprine group (−0.13, SD ±1.05) (MD −0.20, 95% CI −0.52 to −0.13; p=0.242). **(MODERATE)** • One open-label randomised trial (Zhang et al. 2020) showed that statistically significantly more participants in the azathioprine group had a worsening EDSS score compared with the tocilizumab group (RR 3.667, 95% CI 1.603 to 8.387; p=0.0005). **(MODERATE)** After a median treatment duration of 23.8 (IQR 13.0 to 51.1) months: • One retrospective observational study (Ringelstein et al. 2022) showed a reduction in median EDSS score from 4.5 (IQR 3.0 to 7.0) at the start of

	tocilizumab treatment to 3.5 (IQR 2.0 to 6.5) at last follow up on tocilizumab treatment. No statistical analyses were reported. **(VERY LOW)** • One retrospective observational study (Ringelstein et al. 2022) showed that 5/57 (9%) participants had a worsening EDSS score from the start of tocilizumab treatment to the last follow up on tocilizumab treatment. **(VERY LOW)** After a median treatment duration of 34.1 (IQR to 25.5 to 39.3) months: • One retrospective observational study (Yang et al. 2023) showed that 5/65 (7.7%) participants had a worsening EDSS score from the start of tocilizumab treatment to the end of the follow up period during tocilizumab treatment. **(VERY LOW)** **One open-label randomised trial and 2 retrospective observational studies provided very low to moderate certainty evidence that although tocilizumab may not improve disability, it may limit disability progression up to about 34 months.** **Moderate certainty evidence from 1 open-label randomised trial showed that tocilizumab reduced disability progression up to 24 weeks compared with azathioprine; this was statistically significant at 12 weeks. Moderate certainty evidence from the same study showed that statistically significantly fewer participants in the tocilizumab group experienced a worsening EDSS score at up to 90 weeks. Very low certainty evidence from 2 retrospective observational studies showed that fewer than 10% of participants had a worsening EDSS score up to a median treatment duration of about 34 months.** **Moderate certainty evidence from 1 open-label randomised trial showed a small reduction in mean EDSS score of 0.32 at up to 90 weeks with tocilizumab, but it is unknown if this is clinically meaningful. There was also no difference between the tocilizumab and azathioprine groups. Very low certainty evidence from 1 retrospective observational study showed a reduction in median EDSS score of 1.0 after about 23 months of tocilizumab, but no statistical analyses were reported.**
Measure of disability in people with NMOSD or MOGAD: Visual acuity **Certainty of evidence:** Very low to moderate	This outcome is important to patients because a measure of disability progression will likely be associated with a significant reduction in quality of life. **Visual acuity** One open-label randomised trial (Zhang et al. 2020) provided evidence for outcomes on visual acuity. Assessments were undertaken of low-contrast letter scores measured with a retro-illuminated 2.5% Sloan letter chart and best corrected high-contrast Logarithm of the Minimum Angle of Resolution (LogMAR) visual acuity measured using a retro-illuminated Early Treatment Diabetic Retinopathy Study chart at 2.52 m. Between baseline and at 60 weeks: • One open-label randomised trial (Zhang et al. 2020) showed no significant difference in LogMAR visual acuity between the tocilizumab and azathioprine groups in either affected (MD −0.0095, 95% CI −0.0191 to −0.0002; p=0.0558) or unaffected (MD 0.0012, 95% CI −0.0032 to 0.0056; p=0.5796) eyes. **(MODERATE)** A decrease in LogMAR visual acuity represents recovery of vision. • One open-label randomised trial (Zhang et al. 2020) showed no significant difference in high-contrast letter score between the tocilizumab and azathioprine groups in either affected (MD 0.3553, 95% CI −0.0833 to 0.7938;

	p=0.1110) **(MODERATE)** or unaffected (MD 0.0034, 95% CI −0.0300 to 0.0367; p=0.8398) eyes (exploratory outcome). **(VERY LOW)** An increase in high-contrast letter score represents recovery of vision. • One open-label randomised trial (Zhang et al. 2020) showed no significant difference in low-contrast letter score between the tocilizumab and azathioprine groups in either affected (MD 0.1113, 95% CI −0.0078 to 0.2304; p=0.0667) **(LOW)** or unaffected (MD 0.0164, 95% CI 0.0292 to 0.1415; p=0.4190) eyes (exploratory outcome). **(MODERATE)** An increase in low-contrast letter score represents recovery of vision. At an unspecified timepoint: • One open-label randomised trial (Zhang et al. 2020) showed a statistically significant lower risk of optic neuritis attacks in the tocilizumab group (1 attack in affected eyes and no attacks in unaffected eyes) compared with the azathioprine group (3 attacks in the affected eyes and 6 attacks in the unaffected eyes) (HR 0.182, 95% CI 0.049 to 0.677; p=0.011). **(MODERATE)** Note, optic neuritis was also one of the criteria that was used to define a relapse. **One open-label randomised trial provided very low to moderate certainty evidence that tocilizumab did not have a beneficial impact on LogMAR, high-contrast or low-contrast visual acuity at 60 weeks, compared with azathioprine. However, moderate certainty evidence from the same trial showed a statistically significant lower risk of optic neuritis with tocilizumab.**
Symptom alleviation in people with NMOSD or MOGAD **Certainty of evidence:** Very low	This outcome is important to patients because reduction in symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. Two retrospective observational studies provided evidence for symptom alleviation. Both studies provided evidence on the impact of tocilizumab on participant's pain after a median treatment duration of 23.8 (IQR 13.0 to 51.1) months in the Ringelstein et al. 2022 study and 34.1 (IQR 25.5 to 39.3) months in the Yang et al. 2023 study. After a median treatment duration of 23.8 (IQR 13.0 to 51.1) months: • One retrospective observational study (Ringelstein et al. 2022) showed that 25/52 (48%) participants on tocilizumab still had chronic pain with a median intensity of 2.0 (IQR 1 to 3, data from 24 participants) and that there was no change from baseline, when 28/51 (55%) reported chronic pain with a median intensity of 2.0 (IQR 1 to 3, data from 27 participants). **(VERY LOW)** Chronic pain was measured as occurrence and intensity and was classified as mild = 1, moderate = 2 and severe = 3. After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: • One retrospective observational study (Yang et al. 2023) showed that in 34/65 (52%) participants who reported chronic pain before tocilizumab treatment, median pain intensity scores increased to 2.5 (IQR 1.5 to 4.0) from 2 (IQR 1.5 to 3.5) at baseline. No statistical analyses were reported. **(VERY LOW)** Participants were asked to report on NMOSD-related pain (i.e. pain related to myelitis) and it was assessed using a numerical rating scale rated between 0 (no pain) to 10 (worst pain imaginable).

	Very low certainty evidence from 2 retrospective observational studies showed that tocilizumab did not improve chronic pain up to a median duration of about 34 months, but no statistical analyses were reported. It is unclear if validated pain tools were used and whether they were sensitive enough to detect change.
Important outcomes	
Health related quality of life	This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived wellbeing and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. No evidence was identified for this outcome.
Hospitalisations / hospital appointments	This outcome is important to patients and their carers because a reduction in number and length of hospitalisations or hospital appointments may indicate that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention. No evidence was identified for this outcome.
Steroid reduction	This outcome is important to those patients receiving corticosteroids because corticosteroid treatment is linked with iatrogenic health problems including osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders. No evidence was identified for this outcome.
Safety	
Frequency of adverse events in people with NMOSD or MOGAD **Certainty of evidence:** Very low and moderate	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects (AEs) of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. One open-label randomised trial **(**Zhang et al. 2020) and 2 retrospective observational studies (Ringelstein et al. 2022; Yang et al. 2023) provided evidence relating to the frequency of adverse events during tocilizumab treatment. The follow up period varied by study from up to 90 weeks for the randomised trial, to a follow up after a tocilizumab median treatment duration of 23.8 (IQR 13.0 to 51.1) months in the Ringelstein et al. 2022 study and 34.1 months (IQR 25.5 to 39.3 months) in the Yang et al. 2023 study. None of the studies reported any statistical analyses. In Zhang et al. 2020: • The incidence of adverse events was similar between the tocilizumab (57/59, 97%) and azathioprine (56/59, 95%) groups, and most were classified as mild. **(MODERATE)** • The most common adverse events were increased alanine transaminase concentrations (18/59, 31% in the tocilizumab group compared with 27/59, 46% in the azathioprine group), upper respiratory tract infection (17/59, 29% in the tocilizumab group compared with 23/59, 39% in the azathioprine group) and urinary tract infections (17/59, 29% in the tocilizumab group compared with 21/59, 36% in the azathioprine group). (**MODERATE**) • Grade 3 (severe) and grade 4 (life-threatening) adverse events were higher in the azathioprine group (21/59, 36%) than in the tocilizumab group (9/59, 15%). (**MODERATE**)

	• The incidence of serious adverse events was higher in the azathioprine group (9/59, 15%) than in the tocilizumab group (5/59, 8%). (**MODERATE**) In Ringelstein et al. 2022: • Of the selected adverse events reported, the following occurred in at least 10% of participants in the study: transient and mild to moderate liver enzyme change (20/57, 35%), neutropenia (10/57, 17%), upper respiratory tract infections, colds, bronchitis or pneumonia (9/57, 16%), recurrent urinary tract infections (9/57, 16%) and infusion-related reactions (7/57, 12%). **(VERY LOW)** In Yang et al. 2023: • Of the selected adverse events reported, 28/65 (43%) participants had mild to moderate increases in serum alanine transaminase level. Infections occurred in 18/65 (27.7%), including urinary tract (n=11), upper respiratory tract (n=8), zoster virus (n=4), and pneumonia (n=3). Infusion-related reactions occurred in 5/65 (7.7%), including skin rash (n=2), lower limb oedema (n=2), headache (n=1), dizziness (n=1) and hypotension (n=1). Transient fatigue, lasting a mean 3.4 days (range 1 to 9 days), occurred in 15/65 (23.1%) participants and 7/65 (10.7%) had hypercholesterolaemia. **(VERY LOW)** **Moderate certainty evidence from 1 open-label randomised trial showed that most participants (about 95%) experienced adverse events with both tocilizumab and azathioprine, and they were mainly mild. Moderate certainty evidence from the same study and very low certainty evidence from 2 retrospective observational studies showed that the reported adverse events included raised liver enzyme levels, upper respiratory and urinary tract infections, and infusion-related reactions. Serious, severe, and life-threatening events were lower in participants receiving tocilizumab compared with azathioprine, but no statistical analyses were reported.**
Adverse events leading to discontinuation in people with NMOSD or MOGAD **Certainty of evidence:** Very low and moderate	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects (AEs) of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. One open-label randomised trial **(**Zhang et al. 2020) and 1 retrospective observational study (Ringelstein et al. 2022) provided evidence relating to adverse events leading to discontinuation of study drug. The follow up period varied by study from up to 90 weeks for the randomised trial, to a follow up after a tocilizumab median treatment duration of 23.8 (IQR 13.0 to 51.1) months in the Ringelstein et al. 2022 study. Neither study reported any statistical analyses. In Zhang et al. 2020: • Adverse events led to discontinuation of a study drug in 1/59 (2%) of the tocilizumab group (due to an acute haemorrhagic stroke) and 2/59 (3%) of the azathioprine group (due to severe hepatic dysfunction and following severe myelosuppression). **(MODERATE)** In Ringelstein et al. 2022: • Tocilizumab was discontinued in 5/57 (9%) participants, due to suspected side effects. **(VERY LOW)** **Moderate certainty evidence from 1 open-label randomised trial and very low certainty evidence from 1 retrospective observational study showed that adverse events leading to discontinuation of the study drug were low (occurring in less than 10% of participants) and were similar between the**

	tocilizumab and azathioprine groups, but no statistical analyses were reported.
Mortality in people with NMOSD or MOGAD **Certainty of evidence:** Very low and moderate	One open-label randomised trial **(**Zhang et al. 2020) and 1 retrospective observational study (Ringelstein et al. 2022) provided evidence relating to mortality. The follow up period varied by study from up to 90 weeks for the randomised trial, to a follow up after a tocilizumab median treatment duration of 23.8 (IQR 13.0 to 51.1) months the Ringelstein et al. 2022 study. Neither study reported any statistical analyses. In Zhang et al. 2020, 2 deaths were reported (1 in each of the tocilizumab and azathioprine groups) which occurred during the study; neither was considered treatment or study drug related. In the azathioprine group, the death was caused by severe intracranial infection and cerebral oedema. In the tocilizumab group, the death was due to central respiratory failure secondary to myelitis. (**MODERATE**) In Ringelstein et al. 2022, 1 death due to recurrent pneumonia was reported, which occurred 2 months after discontinuation of a 6-month tocilizumab treatment period, it was considered unrelated to tocilizumab treatment. (**VERY LOW**) **Moderate certainty evidence from 1 open-label randomised trial and very low certainty evidence from 1 retrospective observational study suggests that tocilizumab does not have an impact on mortality in participants with NMOSD. However, these studies may have been too small or too short to detect rare events.**

Abbreviations

AQP4-IgG, aquaporin-4 water antibodies; ARR, annualised relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; IQR, interquartile range; LogMAR, Logarithm of the Minimum Angle of Resolution; MOG, myelin oligodendrocyte glycoprotein; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MD, mean difference; NMOSD, neuromyelitis optica spectrum disorder; RR, relative risk; SD, standard deviation.

In patients with NMOSD or MOGAD who are intolerant to or whose disease is refractory to previous lines of therapy, what is the cost effectiveness of tocilizumab compared with current standard of care or best supportive care?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for this outcome.

From the evidence selected, are there any subgroups of patients that may benefit from tocilizumab more than the wider population of interest?

Prespecified subgroups

Subgroup	Evidence statement
People with AQP4-IgG positive NMOSD	**Relapse rate** One open-label randomised trial (Zhang et al. 2020, n=103) provided evidence for relapse rate in participants with AQP4-IgG positive NMOSD at up to 90 weeks. Two retrospective observational studies (Ringelstein et al. 2022, n=36; Yang et al. 2023, n=54) provided evidence for relapse rate and disability. Ringelstein et al. 2022 reports the median duration of tocilizumab received by participants with AQP4-IgG positive NMOSD (27.9 months, IQR 12.9 to 53.2 months). Yang et el. 2023 does not report the median treatment duration

for their AQP4-IgG positive NMOSD population, so the median treatment duration for the entire cohort (34.1 months, IQR 25.5 to 39.3 months) is reported in this section.

Risk of relapse
At up to 90 weeks:

- One open-label randomised trial (Zhang et al. 2020) showed that the risk of relapse was statistically significantly lower in the tocilizumab group (6/50 relapses, 12%) compared with the azathioprine group (25/53 relapses, 47%) (HR 0.202, 95% CI 0.083 to 0.493; p=0.0004).

Time to relapse
- One retrospective observational study (Ringelstein et al. 2022) showed that the median time to first relapse on tocilizumab was 4.4 (range 0.5 to 47) months.

- One retrospective observational study (Yang et al. 2023) showed that the median time to first relapse on tocilizumab was 18.6 months.

Percentage relapse free
After a median treatment duration of 27.9 (IQR 12.9 to 53.2) months:

- One retrospective observational study (Ringelstein et al. 2022) reported that 20/36 (56%) participants on tocilizumab were relapse free.

After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months:

- One retrospective observational study (Yang et al. 2023) reported that 41/54 (75.9%) participants on tocilizumab were relapse free.

Annualised relapse rate (ARR)
After a median treatment duration of 27.9 (IQR 12.9 to 53.2) months:

- One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median ARR (0, range 0 to 4.2) compared with the 2-year baseline period prior to tocilizumab treatment (1.5, range 0 to 5) (p<0.001, 95% CI 0 to 0.2).

After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months:

- One retrospective observational study (Yang et al. 2023) showed a statistically significant reduction in median ARR (0.14) compared with before tocilizumab treatment (1.89) (p<0.0001, 95% CI 1.38 to 2.12).

One open-label randomised trial and 2 retrospective observational studies showed that in participants with AQP4-IgG positive NMOSD, relapse rate was statistically significantly reduced with tocilizumab compared with azathioprine at up to 90 weeks and compared with before tocilizumab treatment up to a median treatment duration of 34.1 months. However, in 1 retrospective observational study, the range of ARRs reported were wide, indicating high variability in the results.

Measure of disability

After a median treatment duration of 27.9 (IQR 12.9 to 53.2) months:

- One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median EDSS score from 6.25 (IQR 3.0 to 7.6) at the start of tocilizumab treatment to 4.25 (IQR 2.5 to 7.0) at last follow up on tocilizumab treatment (p<0.003).

- One retrospective observational study (Ringelstein et al. 2022) showed that 3/36 (8%) participants had a worsening EDSS score from the start of tocilizumab treatment to the last follow up on tocilizumab treatment.

After a median treatment duration of 34.1 (IQR to 25.5 to 39.3) months:

- One retrospective observational study (Yang et al. 2023) showed a statistically significant reduction in median EDSS score from 5.75 (range 1 to 8.5) at the start of tocilizumab treatment to 3.5 (range 0 to 8) at last follow up on tocilizumab treatment ($p<0.001$).

- One retrospective observational study (Yang et al. 2023) showed that 4/54 (7.4%) participants had a worsening EDSS score from the start of tocilizumab treatment to the end of the follow up period during tocilizumab treatment.

Two retrospective observational studies showed that in participants with AQP4-IgG positive NMOSD, there were statistically significant reductions in median EDSS score compared with before tocilizumab treatment, up to a median treatment duration of about 34 months. However, it is unknown if these reductions are clinically meaningful. The range of EDSS scores are also very wide in both studies, indicating high variability in the results.

Safety

One retrospective observational study (Ringelstein et al. 2022) provided evidence for the safety of tocilizumab in participants with AQP4-IgG positive NMOSD (n=36). The follow up period was after a tocilizumab median treatment duration of 27.9 (IQR 12.9 to 53.2) months. No statistical analyses were reported.

Frequency of adverse events
Ringelstein et al. 2022 reported the following selected adverse events (occurring in at least 10% of all participants in the study) in participants with AQP4-IgG positive NMOSD: transient and mild to moderate liver enzyme change (12/36, 33%), neutropenia (8/36, 22%), recurrent urinary tract infections (7/36, 19%), infusion related reactions (6/36, 17%) and upper respiratory tract infections, colds, bronchitis or pneumonia (5/36, 14%).

Adverse events leading to discontinuation
Ringelstein et el. 2022 reported that tocilizumab was discontinued in 5/36 (14%) participants with AQP4-IgG positive NMOSD due to suspected side effects such as ileus (n=1), nephritis and urticaria in the context of systemic lupus erythematosus (n=1), psoriasis exacerbation (n=1) and upper respiratory tract infection (n=3).

Mortality
Ringelstein et al. 2022 reported that 1 death occurred in someone with AQP4-IgG positive NMOSD (1/36, 3%), which was considered unrelated to tocilizumab treatment by the physician.

One retrospective observational study showed that the safety profile of tocilizumab in participants with AQP4-IgG positive NMOSD is comparable to that in the wider study population. However, this study may have been too small or too short to detect rare events, such as death or discontinuations.

People with AQP4-IgG negative NMOSD	**Relapse rate** One open-label randomised trial (Zhang et al. 2020, n=15) provided evidence for relapse rate in participants with AQP4-IgG negative NMOSD at up to 90 weeks. Two retrospective observational studies (Ringelstein et al. 2022, n=7; Yang et al. 2023, n=11) provided evidence for relapse rate and disability in participants with AQP4-IgG negative NMOSD. Ringelstein et al. 2022 reports the median duration of tocilizumab received by participants with AQP4-IgG negative NMOSD (30.4 months, IQR 10.3 to 38.1 months). Yang et el. 2023 does not report the median treatment duration for their AQP4-IgG negative NMOSD population, so the median treatment duration for the entire cohort (30.4 months, IQR 10.3 to 38.1 months) is reported in this section. **Risk of relapse** At up to 90 weeks: • One open-label randomised trial (Zhang et al. 2020) showed no significant difference in the risk of relapse between the tocilizumab group (2/9, 22%) and the azathioprine group (3/6, 50%) (HR 0.470, 95% CI 0.078 to 2.821; p=0.408). Note, Zhang et al. 2020 included participants with MOGAD (n=3) in the AQP4-IgG negative NMOSD group. **Time to relapse** One retrospective observational study (Ringelstein et al. 2022) showed that the median time to first relapse was 12.2 (range 2.6 to 18.9) months. One retrospective observational study (Yang et al. 2023) showed that the median time to first relapse was 15.5 months. **Percentage relapse free** After a median treatment duration of 30.4 (IQR 10.3 to 38.1) months: • One retrospective observational study (Ringelstein et al. 2022) showed that 3/7 (43%) participants were relapse free. After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: • One retrospective observational study (Yang et al. 2023) showed that 9/11 (81.8%) participants were relapse free. **Annualised relapse rate (ARR)** After a median treatment duration of 30.4 (IQR 10.3 to 38.1) months: • One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median ARR (0.2, range 0 to 2.0) compared with the 2-year baseline period prior to tocilizumab treatment (3.0, range 1.0 to 3.0) (p<0.032, 95% CI 0.3 to 2.8). After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: • One retrospective observational study (Yang et al. 2023) showed a statistically significant reduction in median ARR (0.06) compared with before tocilizumab treatment (1.75) (p<0.0001, 95% CI 1.22 to 2.49). **One open-label randomised trial showed no significant difference in the risk of relapse between tocilizumab and azathioprine in participants with AQP4-IgG negative NMOSD. However, the 2 retrospective observational studies showed statistically significant reductions in median ARR compared with before tocilizumab treatment. The number of participants**

with AQP4-IgG negative NMOSD in these studies may be too small to draw definitive conclusions.

Measure of disability

After a median treatment duration of 30.4 (IQR 10.3 to 38.1) months:

- One retrospective observational study (Ringelstein et al. 2022) showed no significant difference in the median EDSS score at the start of tocilizumab treatment (5.0, IQR 4.5 to 5.8) to the median EDSS score at last follow up on tocilizumab treatment (5.0, IQR 3.5 to 6.8) ($p<0.77$).

- One retrospective observational study (Ringelstein et al. 2022) showed that 2/7 (29%) participants had a worsening EDSS score from the start of tocilizumab treatment to the last follow up on tocilizumab treatment.

After a median treatment duration of 34.1 (IQR to 25.5 to 39.3) months:

- One retrospective observational study (Yang et al. 2023) showed a statistically significant reduction in median EDSS score from 5 (range 1.5 to 6.0) at the start of tocilizumab treatment to 2.5 (range 0 to 5.5) at last follow up on tocilizumab treatment ($p=0.043$).

- One retrospective observational study (Yang et al. 2023) showed that 1/11 (9.1%) participants had a worsening EDSS score from the start of tocilizumab treatment to the end of the follow up period during tocilizumab treatment.

Two retrospective observational studies provided evidence on the outcome of disability in participants with AQP4-IgG negative NMOSD, but the results are inconsistent. The number of participants with AQP4-IgG negative NMOSD in these studies may be too small to draw definitive conclusions.

Safety

One retrospective observational study (Ringelstein et al. 2022) provided evidence for the safety of tocilizumab in participants with AQP4-IgG negative NMOSD (n=7). The overall follow up period was after a tocilizumab median treatment duration of 30.4 (IQR 10.3 to 38.1) months. No statistical analyses were reported.

Frequency of adverse events
Ringelstein et al. 2022 reported the following selected adverse events (occurring in at least 10% of all participants in the study) in participants with AQP4-IgG negative NMOSD: transient and mild to moderate liver enzyme change (6/7, 86%), upper respiratory tract infections, colds, bronchitis or pneumonia (2/7, 29%), recurrent urinary tract infections (1/7, 14%). There were no reports of infusion related reactions or neutropenia in participants with AQP4-IgG negative NMOSD.

Adverse events leading to discontinuation
Ringelstein et al. 2022 reported that tocilizumab was not discontinued due to side effects in any participants with AQP4-IgG negative NMOSD.

Mortality
Ringelstein et al. 2022 reported that no deaths occurred in participants with AQP4-IgG negative NMOSD.

One retrospective observational study showed that the safety profile of tocilizumab in participants with AQP4-IgG negative NMOSD is comparable to that in the wider study population. However, this study may have been

	too small or too short to detect rare events, such as death or discontinuations.
People with MOGAD	## Relapse rate One open-label randomised trial (Zhang et al. 2020, n=3) provided evidence for relapse rate in participants with MOGAD at up to 90 weeks. One retrospective observational study (Ringelstein et al. 2022, n=14) provided evidence for relapse rate and disability in participants with MOGAD at up to a median treatment duration of 16.3 (IQR 14.2 to 44.6) months. **Time to relapse** • One retrospective observational study (Ringelstein et al. 2022) showed that the median time to first relapse on tocilizumab was 9.4 months (range 9 to 15 months). **Percentage relapse free** At up to 90 weeks: • One open-label randomised trial (Zhang et al. 2020) showed that 1/1 (100%) participant in the tocilizumab group was relapse free compared with 1/2 (50%) in the azathioprine group. No statistical analyses were reported. After a median treatment duration of 16.3 (IQR 14.2 to 44.6) months: • One retrospective observational study (Ringelstein et al. 2022) showed that 11/14 (79%) participants on tocilizumab were relapse free. **Annualised relapse rate (ARR)** After a median treatment duration of 16.3 (IQR 14.2 to 44.6) months: • One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median ARR (0, range 0 to 0.9) compared with the 2-year baseline period prior to tocilizumab treatment (1.75, range 0.5 to 5) ($p<0.0011$, 95% CI 1.3 to 2.6). **One open-label randomised trial provided evidence for relapse rate in participants with MOGAD but no statistical analyses were carried out. Very low certainty evidence from 1 retrospective observational study showed a statistically significant reduction in ARR with tocilizumab. The number of participants in these studies may be too small to draw meaningful conclusions.** ## Measure of disability One retrospective observational study (Ringelstein et al. 2022) provided evidence for disability in participants with MOGAD, measured after a median treatment duration of 16.3 months. After a median treatment duration of 16.3 (IQR 14.2 to 44.6) months: • One retrospective observational study (Ringelstein et al. 2022) showed a statistically significant reduction in median EDSS score from 2.75 (IQR 2.0 to 3.5) at the start of tocilizumab treatment to 2.0 (IQR 1.2 to 2.9) at last follow up on tocilizumab treatment ($p<0.031$). • One retrospective observational study (Ringelstein et al. 2022) showed that 0/14 (0%) participants had a worsening EDSS score from the start of tocilizumab treatment to the last follow up on tocilizumab treatment.

	One retrospective observational study showed that in participants with MOGAD, there was a statistically significant reduction in median EDSS score compared with before tocilizumab treatment, up to a median treatment duration of about 16 months. However, it is unknown if this reduction is clinically meaningful. The same study also showed that none of the participants with MOGAD experienced a worsening EDSS score, but the number of participants with MOGAD included in this study may be too small to draw definitive conclusions. **Safety** One retrospective observational study (Ringelstein et al. 2022) provided evidence for the safety of tocilizumab in participants with MOGAD (n=14). The overall follow up period was after a tocilizumab median treatment duration of 16.3 (IQR 14.2 to 44.6) months. No statistical analyses were reported. **Frequency of adverse events** Ringelstein et al. 2022 reported the following selected adverse events (occurring in at least 10% of all participants in the study) in participants with MOGAD: transient and mild to moderate liver enzyme change (2/14, 14%), upper respiratory tract infections, colds, bronchitis or pneumonia (2/14, 14%); neutropenia (2/14, 14%), infusion related reactions (1/14, 7%); recurrent urinary tract infections (1/14, 7%). **Adverse events leading to discontinuation** Ringelstein et al. 2022 reported that tocilizumab was not discontinued due to side effects in any participants with MOGAD. **Mortality** Ringelstein et al. 2022 reported that no deaths occurred in anyone with MOGAD. **One retrospective observational study showed that the safety profile of tocilizumab in participants with MOGAD is comparable to that in the wider study population. However, this study may have been too small or too short to detect rare events, such as death or discontinuations.**
Comparing people with AQP4-IgG positive NMOSD and AQP4-IgG negative NMOSD	One retrospective observational study (Yang et al. 2023) included some direct comparisons between participants with positive (n=54) and negative (n=11) AQP4-IgG NMOSD, after a median treatment duration of 34.1 (IQR 25.5 to 39.3) months. • There was no significant difference in the median ARR after treatment between participants with AQP4-IgG positive NMOSD (0.14) and AQP4-IgG negative NMOSD (0.06) p=0.3618. • There was no significant difference in the median times to first relapse between participants with AQP4-IgG positive NMOSD (18.6 months) and AQP4-IgG negative NMOSD (15.5 months) p=0.7210. One retrospective observational study (Ringelstein et al. 2022) included some direct comparisons between participants with positive (n=36) and negative (n=7) AQP4-IgG NMOSD, after a median treatment duration of 23.8 (IQR 13.0 to 51.1) months. • The AQP4-IgG negative NMOSD group had on average 2.6 times the relapse counts compared with the AQP4-IgG positive NMOSD group (p<0.03). **Two retrospective observational studies provided evidence on the difference in relapse rates between participants with AQP4-IgG positive and AQP4-IgG negative NMOSD treated with up to a median duration of**

	about 34 months tocilizumab. However, the results are inconsistent, and no conclusions can be drawn.
Comparing people with MOGAD and AQP4-IgG positive NMOSD	One retrospective observational study (Ringelstein et al. 2022) included some direct comparisons between participants with AQP4-IgG positive NMOSD (n=36) and participants with MOGAD (n=14), after a median treatment duration of 23.8 (IQR 13.0 to 51.1) months. • Relapses occurred 8% less in MOGAD participants compared with participants with AQP4-IgG positive NMOSD, but this was not statistically significant (p=0.86). **One retrospective observational study showed no statistically significant difference in the relapse rate between participants with MOGAD and AQP4-IgG positive NMOSD treated with a median duration of about 23 months tocilizumab.**

Abbreviations

AQP4-IgG, aquaporin-4 water antibodies; ARR, annualised relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; EMA, European Medicines Agency; HR, hazard ratio; IQR, interquartile range; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder.

Additional subgroups

Subgroup	Evidence statement
People with NMOSD or MOGAD who used concomitant immunosuppressants, including corticosteroids	In 1 retrospective observational study (Yang et al. 2023), 59/65 (90.7%) participants were taking oral prednisone at a median dose of 25 mg (range 15 to 40 mg) when starting tocilizumab. The prednisone was tapered and discontinued within a median of 4.2 (range 3 to 8) months. Tocilizumab was used as monotherapy from the start in 6/65 (9.2%) participants. After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: • Of 59 participants receiving concomitant corticosteroids when starting tocilizumab, 48 (81%) were relapse free, compared with 2/6 (33%) participants who were given tocilizumab as monotherapy at initiation. No statistical analyses were reported. • Median ARR decreased from 1.95 to 0.09 (p<0.0001, 95% CI 1.51 to 2.21) in those receiving concomitant corticosteroids, compared with from 1.48 to 0.49 (p=0.0495, 95% CI 0.05 to 2.02) in the monotherapy group. The ARR after treatment was statistically significantly lower in those receiving concomitant corticosteroids (p=0.0005). In 1 retrospective observational study (Ringelstein et al. 2022), 20/57 (35%) participants received tocilizumab as an add-on treatment with other immunosuppressants. In 2 participants, this was due to comorbidities. Additional medicines included low dose corticosteroids (n=10), methotrexate (n=4), mycophenolate mofetil (n=2), azathioprine (n=1), IVIG (n=1), rituximab (n=1) and monthly high dose corticosteroids (n=1). These were administered for less than 6 months in 3 participants and more than 6 months in 17 participants during tocilizumab treatment. After a median treatment duration of 23.8 (IQR 13.0 to 51.5) months: • Of 37 participants given tocilizumab as monotherapy, 29 (78%) were relapse free during treatment, compared with 8/20 (40%) participants receiving add-on treatment. No statistical analyses were reported.

	• Median ARR decreased in participants who were given tocilizumab as monotherapy (n=37), from 1.5 (IQR 1 to 2.5) to 0 (IQR 0 to 0) compared with the 2-year baseline period prior to tocilizumab treatment. In the add-on group, median ARR reduced from 2.0 (IQR 1 to 3) to 0.2 (IQR 0 to 0.8). No statistical analyses were reported. **One retrospective observational study showed that taking tocilizumab with concomitant corticosteroids statistically significantly decreased median ARR, compared with taking tocilizumab as monotherapy. However, the number of participants receiving tocilizumab monotherapy was low and this finding is very uncertain. Another retrospective observational study, which grouped corticosteroids with other immunosuppressants, showed that 78% of those receiving tocilizumab monotherapy were relapse free compared with 40% of those receiving concomitant immunosuppressants, but no statistical analyses were undertaken.**
Treatment infusion interval in people with NMOSD	One retrospective observational study (Yang et al. 2023) compared different treatment intervals, during a median treatment duration of 34.1 (IQR 25.5 to 39.3) months. In 38/65 (58.5%) participants, infusions were administered every 4 weeks, in 18/65 (27.7%) every 6 weeks and in 7/65 (10.8%) every 8 weeks. After a median treatment duration of 34.1 (IQR 25.5 to 39.3) months: • Median ARR statistically significantly decreased in all groups after treatment (4 weeks from 2.00 to 0.09, p<0.0001, 95% CI 1.59 to 2.23; 6 weeks from 1.55 to 0.18, p=0.0004, 95% CI 0.66 to 2.07; 8 weeks from 2.69 to 0.24, p=0.0225, 95% CI 0.42 to 4.47). • Median times to the first relapse in each group were comparable and not statistically significantly different (4 weeks 17.3 months; 6 weeks 18.8 months; 8 weeks 14 months) p=0.8779. • A logistic regression analysis indicated that an infusion interval of more than 4 weeks increased the relapse risk (OR 10.7, 95% CI 1.6 to 71.4, p=0.014). **One retrospective observational study showed that receiving IV tocilizumab statistically significantly decreased median ARR, regardless of the interval between infusions (4, 6 or 8 weeks), up to a median treatment duration of about 34 months in participants with NMOSD. However, a logistic regression analysis showed that receiving IV tocilizumab at intervals greater than 4 weeks may increase the relapse risk, although the wide confidence intervals around this estimate suggest high variability in this result.**
People with NMOSD or MOGAD who had concomitant autoimmune diseases	One open-label randomised trial (Zhang et al. 2020) carried out a prespecified subgroup analysis of participants with (n=47) and without (n=71) concomitant autoimmune diseases at up to 90 weeks follow up. Direct comparison between participants with and without concomitant diseases, in the full analysis set: • In the tocilizumab group, there was no difference in the risk of relapse between participants with and without concomitant autoimmune diseases (HR 0.419, 95% CI 0.100 to 1.755, p=0.2134), whereas in the azathioprine group, the risk of relapse was higher in participants with concomitant autoimmune disease (HR 0.349, 95% CI 0.1640 to 0.742, p=0.0058). • The median time to first relapse suggested a treatment effect consistent with that of the overall study population, in participants with and without concomitant diseases.

	One retrospective observational study (Yang et al. 2023) compared participants (with NMOSD) with (n=36) and without (n=29) concomitant autoimmune diseases, over a median treatment duration of 34.1 (IQR 25.5 to 39.3) months. • Of participants with concomitant autoimmune diseases, 7/36 (19.4%) relapsed, compared with 8/29 (27.6%) participants without concomitant autoimmune diseases. No statistical analyses were reported. • The median ARR decreased after treatment from 1.73 to 0.17 (p<0.0001, 95% CI 1.05 to 2.06) for participants with concomitant autoimmune diseases and from 2.05 to 0.09 (p<0.0001, 95% CI 1.52 to 2.39) for participants without concomitant autoimmune diseases. The median ARR after treatment did not differ between the 2 groups (p=0.2586). • The median time to first relapse in participants with concomitant autoimmune disease was 20.1 months, and in participants without concomitant autoimmune diseases was 15.8 months. There was no difference between the 2 groups (p=0.5028). **One open-label randomised trial and 1 retrospective observational study showed that concomitant autoimmune diseases do not affect relapse rates on tocilizumab treatment and the time to first relapse in participants with and without concomitant autoimmune diseases were similar to the wider study population.**

Abbreviations

AQP4-IgG, aquaporin-4 water antibodies; ARR, annualised relapse rate; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; IV, intravenous; IVIG, intravenous immunoglobulin; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder; OR, odds ratio.

From the evidence selected, what dose and route of administration of tocilizumab was used?

Study	Dose and route of administration of tocilizumab
Ringelstein et al. 2022	IV tocilizumab at a mean interval of 31.6 (range 26.1 to 44.2) days and with a median dose of 8.0 (range 6.0 to 12.0) mg/kg (in 56 participants). SC tocilizumab given as weekly injections of 162 mg (in 1 participant).
Yang et al. 2023	IV tocilizumab 8 mg/kg at a mean interval of 37.5 (range 27 to 61) days. In 38/65 (58.5%) participants, tocilizumab was administered every 4 weeks at a median interval of 29.5 (range 27 to 31) days; 18/65 (27.7%) received tocilizumab every 6 weeks at a median interval of 45 (range 43 to 47) days; 7/65 (10.8%) received tocilizumab every 8 weeks at a median interval of 58 (range 56 to 61) days.
Zhang et al. 2020	IV tocilizumab 8 mg/kg every 4 weeks.

Abbreviations

SC, subcutaneous; IV, intravenous; mg/kg, milligrams per kilogram.

From the evidence selected, how was NMOSD or MOGAD defined?

Outcome	Evidence statement
Ringelstein et al. 2022	The study included all people with AQP4-IgG positive NMOSD, MOGAD and double-seronegative NMOSD (diagnostic criteria for inclusion was not defined). Baseline characteristics report that 36/57 (63%) fulfilled 2006 diagnostic criteria for neuromyelitis optica (4/14 MOGAD, 27/36 AQP4-IgG positive NMOSD, 5/7 double-seronegative NMOSD). All NMOSD participants (both AQP4-IgG positive and double-seronegative) and 7/14 MOGAD participants fulfilled the 2015 international consensus diagnostic criteria for neuromyelitis optica spectrum disorders at baseline.
Yang et al. 2023	The inclusion criteria for the study were adults diagnosed with NMOSD according to 2015 international consensus diagnostic criteria for neuromyelitis optica spectrum disorder.
Zhang et al. 2020	Eligible people were adults with highly relapsing NMOSD diagnosed according to 2015 international consensus diagnostic criteria for neuromyelitis optica spectrum disorder.

Abbreviations

AQP4-IgG, aquaporin-4 water antibodies; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder.

6. Discussion

This evidence review includes 1 phase 2, open-label, randomised trial (Zhang et al. 2020) and 2 retrospective, before and after, observational studies (Ringelstein et al. 2022; Yang et al. 2023). All 3 studies have some limitations that affect their interpretation.

Quality assessment of Zhang et al. 2020 found a low risk of bias in most domains, but participants and treating physicians were not blinded. As all relapses were adjudicated by a blinded centralised committee, and Expanded Disability Status Scale (EDSS) raters, laboratory personnel and radiologists were also blind, the study was not downgraded for this, but should still be noted as a potential source of bias.

Observational non-comparative studies are subject to bias and the quality assessments of both included studies were rated poor. The design of observational studies mean that participants, physicians and investigators were aware of the treatment being given. It is unclear whether decisions regarding analysis were made before or after the data was collected. Statistical analyses were not always reported and some inaccuracies in these analyses and the reported data were noted. It is unclear if the scales used in Ringelstein et al. 2022 for assessing pain is validated and it is unlikely that it would have been applied consistently over the 9-year study period, across the different centres. Another limitation of both uncontrolled studies is that any changes from before to after treatment, could be a result of regression to the mean, especially if tocilizumab was administered soon after a relapse.

Baseline characteristics of participants across the included studies are broadly similar, although there were differences in baseline EDSS scores. This is a 10-point scale, 0 representing a normal examination, 10 representing death due to multiple sclerosis. Baseline median EDSS scores were similar in Zhang et al. 2020 (4.5) and Ringelstein et al. 2022 (4.5) but higher in Yang et al. 2023 (5.5). A score of 4.5 represents someone who has significant but limited disability, whereas a score of 5.5 reflects severe disability which precludes full daily activities. Therefore, these differences in baseline EDSS scores could represent very different populations. Yang et al. 2023 also had a wide range of baseline EDSS scores (1 to 8.5) which includes both those with mild and more severe disease. This includes some participants who would have been excluded by Zhang et al. 2020, as their inclusion criteria required participants to have an EDSS score of 7.5 or lower.

All included studies were downgraded for indirectness due to concerns around whether the included populations are applicable to the proposed population in UK clinical practice. Two of the studies (Yang et al. 2023; Zhang et al. 2020), had exclusion criteria regarding recent use of other immunosuppressants, and Zhang et al. 2020 also excluded people who had previously relapsed on azathioprine. While these exclusions may be appropriate from a study design perspective, they exclude some of our population of interest, which is those who are refractory to previous lines of therapy. Ringelstein et al. 2022 excluded people with acute disseminated encephalomyelitis, which is a recognised clinical manifestation in people with MOGAD. There is also some uncertainty around the relapsing history of participants. Zhang et al. 2020 required a recent history of relapses. This was not an inclusion criterion in either Ringelstein et al. 2022 or Yang et al. 2023. In Ringelstein et al. 2022, 88% of participants switched to tocilizumab due to ongoing disease activity (relapses) or intolerance, but the remaining 12% were switched to tocilizumab due to concomitant disease or due to developing antibodies against rituximab – these latter participants are not an exact match to the intended population. Participants in Yang et al. 2023 switched ‘mainly due to disease breakthrough or adverse events under other immunosuppressants’ but numbers are not reported. However, both studies report bottom ranges of annualised relapse rate (ARR) near 0, which imply that some participants had not experienced many (or any) relapses in the pre-study period. It is possible that these participants

were intolerant to previous immunosuppressants, rather than refractory, but data is not provided to confirm this.

Tocilizumab was used differently in each study. In Zhang et al. 2020, after the initial 12 weeks when concomitant immunosuppressants were permitted, tocilizumab was given as monotherapy. In Ringelstein et al. 2022, 37/57 (65%) participants received tocilizumab as monotherapy – in the remaining 20/57 (35%), it was given alongside other immunosuppressants. These were mostly low dose corticosteroids (n=10), but 18% of participants also received other immunosuppressants, including methotrexate (n=4), mycophenolate (n=2), azathioprine (n=1), intravenous immunoglobulin (IVIG) (n=1), rituximab (n=1) and monthly high dose corticosteroids (n=1). It is not explicitly stated how long the additional immunosuppressants were taken for, nor did they report outcomes for the cohort who received tocilizumab and corticosteroids separately. In Yang et al. 2023, tocilizumab was given alongside prednisone in 91% of participants, which was tapered and discontinued within 3 to 8 months and thereafter, tocilizumab was given as monotherapy. Prednisone is not licensed in the UK. The proposed place of tocilizumab in therapy is alongside best supportive care, with or without corticosteroids, rather than being added to current standard of care, so some of the administration schedules used may not be relevant to proposed practice. Additionally, Yang et al. 2023 administered IV tocilizumab at intervals of 4, 6 and 8 weeks, whereas Zhang et al. 2020 and Ringelstein et al. 2022 administered IV tocilizumab approximately every 4 weeks. As tocilizumab is not licensed for NMOSD or MOGAD, there is no established regimen, so these differences may provide useful information, but should be noted when making conclusions. IV tocilizumab is currently licensed for rheumatoid arthritis at a dose of 8 mg/kg every 4 weeks, which is in alignment with the administration schedule given to most participants in these studies.

It is unclear in the studies where in the clinical pathway tocilizumab is being used. It is possible it is being positioned differently in each study and it is unclear how this relates to the proposed use of tocilizumab in UK clinical practice. Yang et al. 2023 reports what immunosuppressants were taken before tocilizumab treatment, but other than corticosteroids, it is unclear if all participants were taking other immunosuppressants prior to starting tocilizumab and specific regimens cannot be determined. Zhang et al. 2020 reports the immunosuppressant regimens taken by participants at randomisation – most were taking regimens which are first line in the UK; none were receiving rituximab and 2 were receiving IVIG. Both studies were conducted in East Asia where clinical practice may differ. However, in Ringelstein et al. 2022, a European (including UK) and US study, all participants had previously received rituximab. This may reflect the proposed placement of tocilizumab more accurately than the other studies, that is, as an alternative to IVIG (which is only commissioned in people who have failed on 2 or more previous lines of therapy). However, none of the studies provide information regarding the number of treatments to which participants' disease was refractory, or to which participants were intolerant.

Understandably for this condition, participant numbers were relatively small. This is particularly apparent for the subgroups, specifically the AQP4-IgG negative NMOSD and MOGAD populations, which makes drawing conclusions difficult. There is also some uncertainty around identifying people with MOGAD. Zhang et al. 2020 included people with MOGAD within their AQP4-IgG negative NMOSD population, which should be noted when drawing conclusions on this population. However, it also raises the question of whether participants were systematically tested for MOG antibodies, and whether their AQP4-IgG negative NMOSD population may have included more people with MOGAD than the 3 they identified – this is not clear in the paper. Yang et al. 2023 excluded people with MOGAD but similarly, it is not clear if their population were routinely screened for MOG antibodies or if only those with known MOGAD were excluded. As such, it raises the possibility that their study may also have included people with MOGAD. As MOGAD is only recently emerging as a condition distinct from multiple sclerosis

and NMOSD, it is possible that some of the studies did not routinely test for these antibodies (MOG encephalomyelitis: international recommendations on diagnosis and antibody testing).

Different definitions were used for determining relapse. Yang et al. 2023 and Ringelstein et al. 2022 used the same definition, but Zhang et al. 2020 specified additional caveats. Namely, the relapse had to be preceded by at least 30 days of clinical stability, and there had to be a change in EDSS score. Relapses could also be confirmed by MRI, if the clinical definition was not met. It is possible this definition may have impacted the number of relapses detected, though it is difficult to say definitively what the impact would be. The requirement of a change in EDSS score appears stricter and may reduce the number of relapses detected, but being able to confirm relapses by MRI may increase the number detected. Of the 30 relapses in this trial, 11 did not meet the clinical criteria but were confirmed by MRI. Regardless of the direction of the impact, any differences in defining relapse which informed the primary outcome of all the studies is a limitation.

All studies used the Expanded Disability Status Scale (EDSS) to measure disability, a scale developed for use in multiple sclerosis. While EDSS is used widely in clinical practice in NMOSD and MOGAD, it has not been the subject of a validation study in these populations. The European Medicines Agency (EMA) guidance on the clinical investigation of medicinal products for the treatment of multiple sclerosis warn against using change in EDSS score from baseline as a measure of efficacy in multiple sclerosis. However, a relapse in people with NMOSD or MOGAD may cause more significant disability than a relapse in people with multiple sclerosis. Therefore, a change in EDSS score from baseline, reported by both Zhang et al. 2020 and Ringelstein et al. 2022, may be a more meaningful measure in NMOSD and MOGAD. However, in the absence of a validation study, there is uncertainty as to the amount of clinically meaningful change seen. Zhang et al. 2020 report disability progression at 12 weeks, using a definition of disability progression which is in accordance with the EMA guidance, although 12 weeks is quite short compared to the long-term nature of the conditions. The same guidance states that time to relapse and the ARR are acceptable parameters to assess relapse status in multiple sclerosis and therefore it could be cautiously inferred that these measures are also appropriate in NMOSD and MOGAD. However, Yang et al. 2023 does not report their method for calculating ARR, which makes comparisons of the ARRs difficult. Additionally, time to first relapse does not provide any indication of whether tocilizumab maintains an effect on relapses.

There were only 3 participants under the age of 18 years in Ringelstein et al. 2022 and they did not report outcomes in this group separately, so no conclusions on tocilizumab in this population can be made.

7. Conclusion

This review provides evidence to suggest that relapse rate is reduced in people with NMOSD or MOGAD treated with tocilizumab. Zhang et al. 2020 provides moderate certainty evidence that tocilizumab statistically significantly improved relapse rate compared with azathioprine. Ringelstein et al. 2022 and Yang et al. 2023 provide very low certainty evidence that tocilizumab statistically significantly improved relapse rate compared with before treatment. Similar statistically significant improvements were seen in the AQP4-IgG positive NMOSD population, although there was more variation in these results. In participants with MOGAD or AQP4-IgG negative NMOSD, it is more difficult to draw conclusions, partly due to the small number of participants. Compared with azathioprine, no difference was seen in relapse rate in people with AQP4-IgG negative NMOSD and the numbers of participants with MOGAD was too small to perform statistical analysis. The observational studies, however, did show statistically significant reductions in annualised relapse rate (ARR) in both subgroups. The clinical significance of the reductions is unknown but median ARRs after treatment were close to 0, indicating a paucity of relapses during treatment. However, the range of ARRs after treatment in participants with AQP4-IgG negative NMOSD in the Ringelstein et al. 2022 study was fairly wide, with an upper ARR of 2.

In terms of disability measured using the Expanded Disability Status Scale (EDSS), Zhang et al. 2020 provides moderate certainty evidence and Ringelstein et al. 2022 and Yang et al. 2023 provide very low certainty evidence that disability progression may be limited by tocilizumab in people with NMOSD or MOGAD. In Zhang et al. 2020, statistically significantly fewer participants had disease progression at 12 weeks, compared with azathioprine. A reduction was also seen at 24 weeks, though this was an exploratory outcome and is more uncertain. Although statistically significant improvement in EDSS score was not shown in this trial, this is unlikely to be a key aim of therapy and limiting disability progression will still have a positive impact on people's quality of life. It is more difficult to draw conclusions on the subgroups, due to small numbers and no comparator being available for the relevant outcomes. Nonetheless, statistically significant reductions in EDSS scores from baseline were seen in both studies across all population subgroups, although Ringelstein et al. 2022 did not show a difference in participants with AQP4-IgG negative NMOSD. However, the reductions may not be clinically meaningful and some of the results had high variability. Yang et al. 2023 reported that in their study, EDSS scores increased by less than 1 in acute attacks, indicating that no severe relapses occurred during tocilizumab treatment.

Zhang et al. 2020 was the only study to measure visual acuity and provides very low to moderate certainty evidence that there was no difference between tocilizumab and azathioprine, in participants with NMOSD or MOGAD. However, a statistically significant reduction in optic neuritis attacks was seen in the tocilizumab group compared with azathioprine, which may be impactful for individuals.

Assessment of pain was only undertaken by the 2 retrospective observational trials. They provide very low certainty evidence that tocilizumab did not moderate pain in participants with NMOSD or MOGAD. However, some of the tools and methods used may not have been validated and baseline pain scores were low, limiting the ability to detect differences.

Tocilizumab is licensed in the UK for other autoimmune conditions. This evidence review provides very low to moderate certainty evidence that the safety profile of tocilizumab, when used in people with NMOSD or MOGAD, is similar to that reported for other conditions (tocilizumab summary of product characteristics). Mostly mild adverse events were experienced by study participants. However, statistical analyses on safety outcomes were not undertaken

and both Ringelstein et al. 2022 and Yang et al. 2023 only reported on selected adverse events, so it is difficult to draw firm conclusions.

The 2 retrospective observational studies provide some evidence on direct comparisons between subgroups. They provide limited evidence to suggest there is no difference in relapse rate between participants with MOGAD and participants with AQP4-IgG positive NMOSD when treated with tocilizumab. However, the evidence on comparisons between positive and negative AQP4-IgG NMOSD is inconsistent, so no conclusions can be drawn.

There is limited evidence to show that concomitant corticosteroids may decrease risk of relapse and giving IV tocilizumab at intervals greater than 4 weeks may increase risk of relapse (Yang et al. 2023). The same study and Zhang et al. 2020 provide evidence to show that having a concomitant autoimmune disease does not affect relapse rate in participants being treated with tocilizumab.

Although 1 study (Ringelstein et al. 2022) did not exclude on age, they only had 3 participants who received tocilizumab under the age of 18 years and did not report outcomes for this group, therefore no conclusions on tocilizumab treatment in this population can be made.

No evidence was found:

- for the important outcomes of health related quality of life, hospitalisation or hospital appointments, or corticosteroid reduction.
- to determine whether tocilizumab is a cost-effective treatment for people with NMOSD or MOGAD.

Appendix A PICO document

The review questions for this evidence review are:

1. In patients with neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) who are intolerant to or whose disease is refractory to previous lines of therapy, what is the clinical effectiveness of tocilizumab compared with current standard of care or best supportive care?
2. In patients with NMOSD or MOGAD who are intolerant to or whose disease is refractory to previous lines of therapy, what is the safety of tocilizumab compared with current standard of care or best supportive care?
3. In patients with NMOSD or MOGAD who are intolerant to or whose disease is refractory to previous lines of therapy, what is the cost effectiveness of tocilizumab compared with current standard of care or best supportive care?
4. From the evidence selected, are there any subgroups of patients that may benefit from tocilizumab more than the wider population of interest?
5. From the evidence selected, what dose and route of administration of tocilizumab was used?
6. From the evidence selected, how was NMOSD or MOGAD defined?

P-Population and Indication	All patients with neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) who are intolerant to or whose disease is refractory to previous lines of therapy [There are three subgroups of interest: • Aquaporin-4 water antibody (AQP4 IgG) positive NMOSD • AQP4 IgG negative NMOSD • MOGAD] [Previous therapies may include corticosteroids (prednisolone), azathioprine, mycophenolate, methotrexate, rituximab or immunoglobulin replacement therapy] [Intolerance is defined as having a contra-indication, anaphylaxis or development of autoantibodies to previous lines of therapy] [Refractory disease means that patients continue to relapse despite current therapy. These patients may be described as relapsing or highly relapsing NMOSD/MOGAD]
I-Intervention	Tocilizumab +/- corticosteroids [Intravenous or subcutaneous routes of administration are of interest] [This may be given alongside best supportive care. Best supportive care may include corticosteroids (prednisolone), antipyretics or analgesia]
C-Comparator	Current standard of care +/- corticosteroids

	[This can include: • Azathioprine • Mycophenolate • Methotrexate • Rituximab • Immunoglobulin therapy] OR Best supportive care +/- corticosteroids
O-Outcomes	**<u>Clinical Effectiveness</u>** *Unless stated for the outcome, minimum clinically important differences (MCIDs) are unknown.* *<u>Critical to decision-making:</u>* • **Relapse rate** *This outcome is important to patients because relapse rates contribute to disability progression and may be associated with a significant reduction in quality of life.* [Relapse rate may be reported as annualised relapse rate (ARR), time to relapse, percentage relapse free or relapse rate reduction.] • **Measure of disability** *This outcome is important to patients because a measure of disability progression will likely be associated with a significant reduction in quality of life.* [Tools to measure this may include but are not limited to the Expanded Disability Status Scale (EDSS), visual acuity or The EDMUS Grading Scale (EGS/DSS)] • **Symptom alleviation** *This outcome is important to patients because reduction of symptoms directly improves the patient's quality of life. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment.* [Other terms used to describe or indicate symptom alleviation include but are not limited to description of symptoms including pain, symptomatic response, alleviating disease symptoms. Symptom alleviation seen before six months may be significant to patients.] *<u>Important to decision-making</u>* • **Health related quality of life** *This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of*

	daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. [Examples of quality-of-life tools include but are not limited to QLQ-OV28, QLQ-C30, EQ-5D and SF-36.] • **Hospitalisations/ Hospital appointments** *This outcome is important to patients and their carers because a reduction in number and length of hospitalisations or hospital appointments may indicate that their treatment has been successful. From a service delivery perspective, it reflects the additional demands placed on the health system for the new intervention.* • **Steroid reduction** *This outcome is important to those patients receiving corticosteroids because corticosteroid treatment is linked with iatrogenic health problems including osteoporosis, diabetes, hypertension, obesity, scarring and electrolyte disorders.* **Safety** *These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects (AEs) of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.* [This also includes discontinuation of treatment due to AEs, severity of AEs and frequency/number of AEs.] **Cost effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2014-2024
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search date: 28 February 2024. Results earlier than 2014 were excluded.

Database: Medline ALL

Platform: Ovid

Version: Ovid MEDLINE(R) ALL <1946 to February 27, 2024>

Search date: 28th Feb 2024

Number of results retrieved: 109

Search strategy:

1 (tocilizumab* or RoActemra* or actemra* or atlizumab* or lusinex*).af. (7027)

2 Neuromyelitis Optica/ (4519)

3 Myelin-Oligodendrocyte Glycoprotein/ (3338)

4 (neuromyelitis* or optica* or NMOSD or oligodendrocyte* or MOGAD).tw. (414193)

5 ((devic or "devic's") adj3 (dis* or syndrome*)).tw. (355)

6 or/2-5 (415511)

7 1 and 6 (122)

8 limit 7 to english language (117)

9 animals/ not humans/ (5165959)

10 8 not 9 (116)

11 limit 10 to yr="2014 -Current" (109)

Database: Embase

Platform: Ovid

Version: Embase <1974 to 2024 February 27>

Search date: 28th Feb 2024

Number of results retrieved: 391 (main search); 105 (conferences)

Search strategy:

1 *tocilizumab/ (5745)

2 (tocilizumab* or RoActemra* or actemra* or atlizumab* or lusinex*).af. (29912)

3 1 or 2 (29912)

4 myelin oligodendrocyte glycoprotein/ (6580)

5 myelooptic neuropathy/ (13080)

6 (neuromyelitis* or optica* or myelo optic or myeloptico* or NMOSD or oligodendrocyte* or MOGAD).tw. (404510)

7 ((devic or "devic's") adj3 (dis* or syndrome*)).tw. (533)

8 or/4-7 (408488)

9 3 and 8 (552)

10 limit 9 to english language (542)

11 nonhuman/ not human/ (5390043)

12 10 not 11 (538)

13 limit 12 to yr="2014 -Current" (496)

14 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5851002)

15 13 not 14 (391)

16 13 not 15 (105)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley

Version:

CDSR –Issue 2 of 12, Month year

CENTRAL – Issue 2 of 12, Month year

Search date:

Number of results retrieved: CDSR – 0; CENTRAL – 17

#1 tocilizumab* or RoActemra* or actemra* or atlizumab* or lusinex* 1717

#2 MeSH descriptor: [Neuromyelitis Optica] this term only 89

#3 MeSH descriptor: [Myelin-Oligodendrocyte Glycoprotein] this term only 15

#4 (neuromyelitis* or optica* or NMOSD or oligodendrocyte* or MOGAD):ti,ab,kw 9913

#5 ((devic or "devic's") near/3 (dis* or syndrome*)):ti,ab,kw 3

#6 #2 or #3 or #4 or #5 9913

#7 #1 and #6 with Publication Year from 2014 to 2024, with Cochrane Library publication date Between Jan 2014 and Feb 2024, in Trials 21

#8 (clinicaltrials or trialsearch):so 490208

#9 #7 not #8 17

#10 "conference":pt 236547

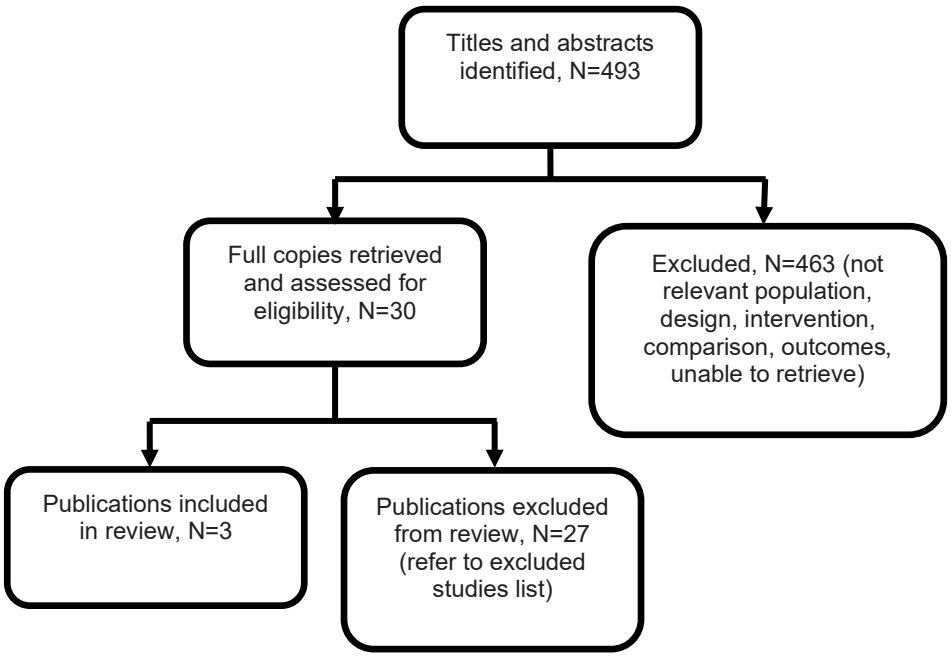
#11 #9 not #10 8

#12 #9 and #10 9 (conferences)

Appendix C Evidence selection

The literature searches identified 493 references. These were screened using their titles and abstracts and 30 references were obtained in full text and assessed for relevance. Of these, 3 references are included in the evidence summary. The remaining 27 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Ringelstein, Marius, Ayzenberg, Ilya, Lindenblatt, Gero et al. (2022) Interleukin-6 Receptor Blockade in Treatment-Refractory MOG-IgG-Associated Disease and Neuromyelitis Optica Spectrum Disorders. Neurology(R) neuroimmunology & neuroinflammation 9(1)	Included
Zhang, Chao, Zhang, Meini, Qiu, Wei et al. (2020) Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial. The Lancet. Neurology 19(5): 391-401	Included
Araki, Manabu, Matsuoka, Takako, Miyamoto, Katsuichi et al. (2014) Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: a pilot study. Neurology 82(15): 1302-6	Excluded – limited number of study participants enrolled, better quality evidence available

Appendix D Excluded studies table

Study reference	Reason for exclusion
Araki, Manabu, Matsuoka, Takako, Miyamoto, Katsuichi et al. (2014) Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: a pilot study. Neurology 82(15): 1302-6	Limited number of study participants enrolled, better quality evidence available
Aungsumart, Saharat, Youngkong, Sitaporn, Dejthevaporn, Charungthai et al. (2023) Efficacy and safety of monoclonal antibody therapy in patients with neuromyelitis optica spectrum disorder: A systematic review and network meta-analysis. Frontiers in neurology 14: 1166490	Data not reported in an extractable format – disaggregated data for tocilizumab not available
Carreon Guarnizo, E, Hernandez Clares, R, Castillo Trivino, T et al. (2022) Experience with tocilizumab in patients with neuromyelitis optica spectrum disorders. Neurologia 37(3): 178-183	Limited number of study participants enrolled, better quality evidence available
Chang, Xuting, Zhang, Jie, Li, Shangru et al. (2023) Meta-analysis of the effectiveness of relapse prevention therapy for myelin-oligodendrocyte glycoprotein antibody-associated disease. Multiple sclerosis and related disorders 72: 104571	Study design – meta-analysis includes case series, better quality evidence available. One relevant study included in this review (Ringelstein et al. 2022)
Du, Chen, Zeng, Pei, Han, Jin-Rui et al. (2021) Early Initiation of Tocilizumab Treatment Against Moderate-to-Severe Myelitis in Neuromyelitis Optica Spectrum Disorder. Frontiers in immunology 12: 660230	Population – unclear if refractory population; intervention introduced during acute attacks
Elsbernd, Paul M, Hoffman, William R, Carter, Jonathan L et al. (2021) Interleukin-6 inhibition with tocilizumab for relapsing MOG-IgG associated disorder (MOGAD): A case-series and review. Multiple sclerosis and related disorders 48: 102696	Study design – better quality evidence available
Garg, S.A., Mathew, T., Sanjee, S. et al. (2023) Tocilizumab in Refractory MOGAD: A real world multicenter experience. Multiple Sclerosis Journal 29(3supplement): 951	Publication type – conference abstract
Kharel, Sanjeev, Shrestha, Suraj, Ojha, Rajeev et al. (2021) Safety and efficacy of interleukin-6-receptor inhibitors in the treatment of neuromyelitis optica spectrum disorders: a meta-analysis. BMC neurology 21(1): 458	Study type – meta-analysis contains abstracts
Kong, Fanxin, Wang, Jianjun, Zheng, Haotao et al. (2021) Monoclonal Antibody Therapy in Neuromyelitis Optica Spectrum Disorders: a Meta-analysis of Randomized Control Trials. Frontiers in pharmacology 12: 652759	Intervention – meta-analysis contains non-relevant interventions, 1 relevant study included in this review (Zhang et al. 2020)
Lallana, J.M., Clares, R.H., Guarnizo, E.C. et al. (2015) Efficacy and safety of tocilizumab as second line therapy in neuromyelitis optica unresponsive to rituximab. Neurology 84(suppl14)	Publication type – conference abstract
Lotan, I., Charlson, R., Ryerson, L.Z. et al. (2020) Effectiveness of subcutaneous tocilizumab therapy in neuromyelitis optica spectrum disorder. Neurology 94(15supplement)	Publication type – conference abstract
Lotan, Itay, Charlson, Robert W, Ryerson, Lana Zhovtis et al. (2020) Effectiveness of subcutaneous tocilizumab in neuromyelitis optica spectrum disorders. Multiple sclerosis and related disorders 39: 101920	Limited number of study participants enrolled, better quality evidence available
Lotan, Itay; McGowan, Richard; Levy, Michael (2021) Anti-IL-6 Therapies for Neuromyelitis Optica Spectrum Disorders: A Systematic Review of Safety and Efficacy. Current neuropharmacology 19(2): 220-232	Study type – review includes abstracts and interim results of a study which are included in this paper in full (Zhang et al. 2020)

Lu, Qianshuo, Luo, Jingjing, Hao, Hongjun et al. (2021) Efficacy and safety of long-term immunotherapy in adult patients with MOG antibody disease: a systematic analysis. Journal of neurology 268(12): 4537-4548	Study type – review includes case reports, better quality evidence available
Luitel, P., Ghimire, A., Upadhyay, D. et al. (2022) Efficacy of monoclonal antibodies in neuromyelitis optica: An updated systematic review with meta-analysis. Clinical and Experimental Neuroimmunology 13(4): 194-207	Study type – review includes abstracts
Mathew, T., Garg, S., Sanjee, S. et al. (2023) Characterizing the Clinical Profile and Treatment Approaches for MOG-associated Disease: A Retrospective Analysis. Annals of Indian Academy of Neurology 26(supplement2): 155	Publication type – conference abstract
Moog, Tatum M, Smith, Alexander D, Burgess, Katy W et al. (2023) High-efficacy therapies reduce clinical and radiological events more effectively than traditional treatments in neuromyelitis optica spectrum disorder. Journal of neurology 270(7): 3595-3602	Data not reported in an extractable format
Rigal, J, Pugnet, G, Ciron, J et al. (2020) Off-label use of tocilizumab in neuromyelitis optica spectrum disorders and MOG-antibody-associated diseases: A case-series. Multiple sclerosis and related disorders 46: 102483	Study type – better quality evidence available
Ringelstein, Marius, Ayzenberg, Ilya, Harmel, Jens et al. (2015) Long-term Therapy With Interleukin 6 Receptor Blockade in Highly Active Neuromyelitis Optica Spectrum Disorder. JAMA neurology 72(7): 756-63	Population – potential overlap of participants in an included paper (Ringelstein et al. 2022)
Shi, F.-D., Zhang, C., Zhang, M. et al. (2019) Tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorders (TANGO): A head-to-head comparative study. Annals of Neurology 86(supplement24): 33	Publication type – conference abstract
Velasco, Mario, Zarco, Luis Alfonso, Agudelo-Arrieta, Mariana et al. (2021) Effectiveness of treatments in Neuromyelitis optica to modify the course of disease in adult patients. Systematic review of literature. Multiple sclerosis and related disorders 50: 102869	Intervention – review contains non-relevant interventions, 1 relevant study included in this review (Zhang et al. 2020)
Wang, Yupeng, Zhao, Mengchao, Yao, Mengyuan et al. (2023) Tocilizumab treatment in neuromyelitis optica spectrum disorders: Updated meta-analysis of efficacy and safety. Multiple sclerosis and related disorders 80: 105062	Publication type – meta-analysis includes a paper excluded due to population
Xie, QinFang, Zheng, Ting, Sun, MengJiao et al. (2020) A meta-analysis to determine the efficacy and safety of tocilizumab in neuromyelitis optica spectrum disorders. Multiple sclerosis and related disorders 45: 102421	Data not reported in an extractable format – data not disaggregated for the main population or subgroups. Individual papers reviewed for inclusion
Xu, Xintong, Xie, Lindan, Wei, Lili et al. (2022) Efficacy and safety of monoclonal antibodies in neuromyelitis optica spectrum disorders: A survival meta-analysis of randomized controlled trials. Advances in ophthalmology practice and research 2(3): 100064	Intervention – review contains non-relevant interventions, 1 relevant study included in this review (Zhang et al. 2020)
Xue, T., Yang, Y., Lu, Q. et al. (2020) Efficacy and Safety of Monoclonal Antibody Therapy in Neuromyelitis Optica Spectrum Disorders: Evidence from Randomized Controlled Trials. Multiple Sclerosis and Related Disorders 43: 102166	Intervention – does not contain a relevant intervention
Xue, Tao, Yu, Jiahao, Chen, Shujun et al. (2020) Different Targets of Monoclonal Antibodies in Neuromyelitis Optica Spectrum Disorders: A Meta-Analysis Evidenced From Randomized Controlled Trials. Frontiers in neurology 11: 604445	Intervention – meta-analysis contains non-relevant interventions, 1 relevant study included in this review (Zhang et al. 2020)

Yin, Ziqian, Qiu, Youjia, Duan, Aojie et al. (2023) Different monoclonal antibodies and immunosuppressants administration in patients with neuromyelitis optica spectrum disorder: a Bayesian network meta-analysis. Journal of neurology 270(6): 2950-2963	Population – unclear if all comparator studies were in the refractory population, 1 relevant study included in this review (Zhang et al. 2020)

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Ringelstein, M, Ayzenberg, I, Lindenblatt, G et al. (2022) **Interleukin-6 Receptor Blockade in Treatment-Refractory MOG-IgG-Associated Disease and Neuromyelitis Optica Spectrum Disorders**. Neurology(R) neuroimmunology & neuroinflammation 9(1) **Study location** Twenty-three tertiary referral centres in Europe (including 1 centre in the UK) and the US. **Study type** Retrospective, before and after, observational study. **Study aim** "To evaluate the long-term safety and efficacy of tocilizumab in myelin oligodendrocyte glycoprotein-IgG associated disease (MOGAD) and neuromyelitis optica spectrum disorders (NMOSD)." **Study dates** The evaluated tocilizumab treatment period was between December 2010 and November 2019.	**Inclusion criteria** People with relapsing MOGAD, classical AQP4-IgG positive NMOSD or double-seronegative NMOSD. **Exclusion Criteria** People with acute disseminated encephalomyelitis. **Total sample size** N=57 No comparator group. **Baseline characteristics** Of the n=57 participants in the study: • 14 (25%) had MOGAD, 36 (63%) had AQP4-IgG positive NMOSD and 7 (12%) had double-seronegative NMOSD • 44 female, 13 male • 50 were Caucasian, 3 African, 3 Arabian and 1 Latin American • the mean (SD) age at the start of tocilizumab treatment was 42.2 (±14.3) years: 3 were under 18 years • the median number of relapses under last immunotherapy was 1.0 (IQR 1.0 to 2.0) • the median EDSS score was 4.5 (IQR 3.0 to 7.0) • all had been treated with immunotherapies prior to tocilizumab treatment and all had received rituximab	**Interventions** IV tocilizumab in 56 participants; mean interval of 31.6 days (range 26.1 to 44.2 days); median dose of 8.0 mg/kg (range 6.0 to 12.0 mg/kg). SC tocilizumab in 1 participant; weekly doses of 162 mg. Tocilizumab was given as add-on therapy in 20/57 (35%), this was due to comorbidities in 2 participants. Median treatment duration 23.8 months (IQR 13.0 to 51.1 months). Thirteen participants had a follow up period of less than 1 year (median 0.5 years) during tocilizumab treatment. The mean (SD) number of tocilizumab infusions given was 34.0 (±28.2). **Comparators** No comparator.	The primary outcome was the ARR. ARR was calculated by dividing the number of attacks within the last 2 years before tocilizumab switch or during tocilizumab treatment time by 2. If a participant had a tocilizumab pretreatment phase of less than 2 years, the number of attacks was categorically divided by 2. If the follow up period was less than 1 year during tocilizumab treatment, the number of attacks was divided by the concrete treatment duration and this measure was extrapolated to 1 year. 'An attack was defined as definitely new neurologic symptom or clear acute worsening of previous neurologic deficits with objective clinical signs, lasting for at least 24 hours and attributed to an inflammatory CNS event, confirmed by the treating physician.' **Critical outcomes** **NMOSD or MOGAD** n=57, median treatment duration 23.8 (IQR 13.0 to 51.1) months. **Relapse rate** **Annualised relapse rate (primary outcome)** Median ARR decreased during tocilizumab treatment compared with the 2-year baseline period prior to tocilizumab treatment, from 1.5 to 0 ($p<0.001$, 95% CI 1.1 to 1.8). **Median time to first relapse** The median time to first relapse in was 9 (range 0.5 to 47) months. **Percentage relapse free** 34/57 (60%) participants were relapse free during tocilizumab treatment. **Measure of disability** Median EDSS score decreased from 4.5 (IQR 3.0 to 7.0) at start of tocilizumab treatment to 3.5 (IQR 2.0 to 6.5) at last follow up during tocilizumab treatment.	This study was appraised using the National Institutes for Health (NIH) quality assessment tool for before-after (pre-post) studies with no control group. 1. Yes 2. No 3. Yes, mostly 4. Unclear 5. Cannot determine 6. Yes 7. Probably not for all outcomes 8. No 9. Yes 10. Only for some outcomes 11. For some participants – not a true time-series design but some data provided to demonstrate multiple measurements were taken (disease course data) 12. Not applicable Quality rating: Poor Other comments: tocilizumab was used as add-on therapy in 20/57 (35%) participants; half of these participants were taking concomitant corticosteroids, the other half were taking other immunosuppressants. People with acute disseminated encephalomyelitis were excluded. Bottom range of median ARR before tocilizumab treatment was between 0 and 1 for the population subgroups, implying some participants may not be highly relapsing. Unclear how eligibility was defined and if all eligible people were enrolled, but discussion

	• 45/57 (79%) switched to tocilizumab due to ongoing disease activity, 5/57 (9%) due to side effects of prior immunotherapies, 6/57 (10%) because of concomitant disease activity and adverse events, 1/57 (2%) had neutralising antibodies against rituximab • 50/57 fulfilled 2015 International diagnostic criteria for NMOSD (36/36 with AQP4-IgG positive NMOSD, 7/7 with double-seronegative NMOSD, 7/14 with MOGAD); 36/57 fulfilled 2006 diagnostic criteria for NMO (27/36 with AQP4 positive NMOSD, 5/7 with double-seronegative NMOSD, 4/14 with MOGAD).		Between tocilizumab initiation and last follow up during tocilizumab treatment, 5/57 (9%) participants had worsening of EDSS score. **Symptom alleviation** In 28/51 (55%) participants who reported initial disease-related chronic pain with a median intensity of 2.0 (IQR 1 to 3; data from 27 participants), presence and intensity of pain were not modulated during tocilizumab treatment, as 25/52 (48%) still had ongoing chronic pain with a median intensity of 2.0 (IQR 1 to 3; data from 24 participants) at last follow up. **Important outcomes** **Health related quality of life** Not reported **Hospitalisations / Hospital appointments** Not reported **Steroid reduction** Not reported **Safety** **Adverse events (AEs)** The following AEs occurred in at least 10% of participants in the study: infusion related reactions (7/57, 12%); recurrent urinary tract infections (9/57, 16%); upper respiratory tract infections, colds, bronchitis or pneumonia (9/57, 16%); neutropenia (10/57, 17%); transient and mild to moderate liver enzyme change (20/57, 35%). **AEs leading to discontinuation** 5/57 (9%) participants discontinued tocilizumab due to suspected side effects. **Mortality** One death due to recurrent pneumonia occurred 2 months after discontinuation of a 6-month tocilizumab treatment period, it was considered unrelated to tocilizumab treatment by the physician. **Prespecified subgroups** Results were reported by AQP4-IgG and MOG status. **AQP4-IgG positive NMOSD**	states they attempted to enrol all people from 2 European cohorts and supplement this with people from additional countries. Sample size appears to be opportunistic rather than predefined and no sample size calculations have been reported. Outcome measure used for pain may not be validated, and unlikely to have been applied consistently across all sites and over the stated time period. None of the investigators or treating physicians were blinded. Case series data has been provided for some participants, demonstrating attack history before and during tocilizumab treatment, over several years in some cases. There were some inaccuracies in the data and statistical analyses reported in the paper. Source of funding: 'The Neuromyelitis Optica Study Group (NEMOS) is partially funded by the German Ministry for Education and Research (BMBF) as part of the German Competence Network Multiple Sclerosis.'

			n=36, median treatment duration 27.9 (IQR 12.9 to 53.2) months. **Critical outcomes** **Relapse rate** **Annualised relapse rate** In participants with AQP4-IgG positive NMOSD, median ARR decreased during tocilizumab treatment compared with the 2-year baseline period prior to tocilizumab treatment, from 1.5 (range 0 to 5) to 0 (range 0 to 4.2) (p<0.001, 95% CI 0 to 0.2). **Time to first relapse** In participants with AQP4-IgG positive NMOSD, the median time to first relapse was 4.4 (range 0.5 to 47) months. **Percentage relapse free** 20/36 (56%) participants with AQP4-IgG positive NMOSD were relapse free during tocilizumab treatment. **Measure of disability** Median EDSS score in participants with AQP4-IgG positive NMOSD decreased from 6.25 (IQR 3.0 to 7.6) before tocilizumab treatment, to 4.25 (IQR 2.5 to 7.0) at last follow up during tocilizumab treatment (p<0.003). Between tocilizumab initiation and last follow up during tocilizumab treatment, 3/36 (8%) participants with AQP4-IgG positive NMOSD had worsening of EDSS score. **Important outcomes** **Safety** **AEs** The following AEs occurred in at least 10% of all participants in the study and occurred at the following frequencies in participants with AQP4-IgG positive NMOSD: infusion related reactions (6/36, 17%); recurrent urinary tract infections (7/36, 19%); upper respiratory tract infections, colds, bronchitis or pneumonia (5/36, 14%); neutropenia (8/36, 22%); transient and mild to moderate liver enzyme change (12/36, 33%). **AEs leading to discontinuations** Tocilizumab was discontinued in 5/36 (14%) participants with AQP4-IgG positive NMOSD due to suspected side effects such as ileus (n=1), nephritis and urticaria in the context of	

			systemic lupus erythematosus (n=1), psoriasis exacerbation (n=1) and upper respiratory tract infection (n=3). **Mortality** One death due to recurrent pneumonia occurred in a participant with AQP4-IgG positive NMOSD (1/36, 3%), after a 6-month tocilizumab treatment period. It was considered unrelated to tocilizumab treatment by the physician. **Double-seronegative NMOSD** n=7, median treatment duration 30.4 (IQR 10.3 to 38.1) months. **Critical outcomes** **Relapse rate** **Annualised relapse rate** In participants with double-seronegative NMOSD, median ARR decreased during tocilizumab treatment compared with the 2-year baseline period prior to tocilizumab treatment, from 3.0 (range 1.0 to 3.0) to 0.2 (range 0 to 2.0) (p<0.032, 95% CI 0.3 to 2.8). **Time to first relapse** In participants with double-seronegative NMOSD, the median time to first relapse was 12.2 (range 2.6 to 18.9) months. **Percentage relapse free** 3/7 (43%) participants with double-seronegative NMOSD were relapse free during tocilizumab treatment. **Measure of disability** Median EDSS score in participants with double-seronegative NMOSD remained stable at 5.0 (IQR 4.5 to 5.8) before tocilizumab treatment, to 5.0 (IQR 3.5 to 6.8) at last follow up during tocilizumab treatment (p<0.77). Between tocilizumab initiation and last follow up during tocilizumab treatment, 2/7 (29%) participants with double-seronegative NMOSD had worsening of EDSS score. **Important outcomes** **Safety** **AEs** The following AEs occurred in at least 10% of all participants in the study and occurred at the following frequencies in	

			participants with double-seronegative NMOSD: recurrent urinary tract infections (1/7, 14%); upper respiratory tract infections, colds, bronchitis or pneumonia (2/7, 29%); transient and mild to moderate liver enzyme change (6/7, 86%). There were no reports of infusion related reactions or neutropenia in participants with double-seronegative NMOSD. **AEs leading to discontinuations** Tocilizumab was not discontinued due to side effects in any participants with double-seronegative NMOSD. **Mortality** No deaths occurred in participants with double-seronegative NMOSD. **MOGAD** n=14, median treatment duration 16.3 (IQR 14.2 to 44.6) months. **Critical outcomes** **Relapse rate** **Annualised relapse rate** In participants with MOGAD, median ARR decreased during tocilizumab treatment compared with the 2-year baseline period prior to tocilizumab treatment, from 1.75 (range 0.5 to 5) to 0 (range 0 to 0.9) (p=0.0011, 95% CI 1.3 to 2.6). **Time to first relapse** In participants with MOGAD, the median time to first relapse was 9.4 (range 9 to 15) months. **Percentage relapse free** 11/14 (79%) participants with MOGAD were relapse free during tocilizumab treatment. **Measure of disability** Median EDSS score in participants with MOGAD decreased from 2.75 (IQR 2.0 to 3.5) before tocilizumab treatment, to 2.0 (IQR 1.2 to 2.9) at last follow up during tocilizumab treatment (p<0.031). Between tocilizumab initiation and last follow up during tocilizumab treatment, none of the participants with MOGAD had worsening of EDSS score. **Important outcomes**	

			Safety **AEs** The following AEs occurred in at least 10% of all participants in the study and occurred at the following frequencies in participants with MOGAD: upper respiratory tract infections, colds, bronchitis or pneumonia (2/14, 14%); neutropenia (2/14, 14%); transient and mild to moderate liver enzyme change (2/14, 14%); infusion related reactions (1/14, 7%); recurrent urinary tract infections (1/14, 7%). **AEs leading to discontinuations** Tocilizumab was not discontinued due to side effects in any participants with MOGAD. **Mortality (not a prespecified outcome)** No deaths occurred in any participants with MOGAD. **Direct comparisons of AQP4-IgG and MOG status** Double-seronegative NMOSD participants had on average 2.6 times the relapse counts compared with AQP4-IgG positive NMOSD participants (p<0.03). In MOGAD participants, relapses occurred 8% less than in AQP4-IgG positive NMOSD participants, but this was not significant (p=0.86). **Cost effectiveness** Not reported	
Full citation Yang, S, Zhang, C, Zhang, T et al. (2023) **A real-world study of interleukin-6 receptor blockade in patients with neuromyelitis optica spectrum disorder**. Journal of neurology 270(1): 348-356 **Study location** China **Study type** Retrospective, before and after, observational study.	**Inclusion criteria** Adults (aged ≥18 years), diagnosed with NMOSD based on the 2015 International diagnostic criteria for NMOSD, who received tocilizumab. **Exclusion Criteria** People were excluded if: • they were treated with other immunosuppressants within expected pharmacodynamics effect window prior to tocilizumab initiation • they had B-cell count less than the lower limit of	**Interventions** IV tocilizumab 8 mg/kg; mean interval of 37.5 (range 27 to 61) days. Planned infusion intervals were 4, 6 and 8 weeks. Median follow up 34.1 (IQR 25.5 to 39.3) months. All participants discontinued prior immunosuppressants, except oral corticosteroids, at tocilizumab initiation. 59/65 (90.8%) were taking oral prednisone at a median dose of 25 mg (range 15 to 40 mg) at time of tocilizumab initiation – these were gradually tapered and discontinued within a median of 4.2 months (range 3 to	The primary outcome was the ARR. Method of calculating ARR was not reported. Relapse was defined as new neurologic symptoms or acute worsening of previous neurologic deficits with objective clinical signs lasting for at least 24 hours and attributed to an inflammatory central nervous system event. **Critical outcomes** **Relapse rate** **Annualised relapse rate (primary outcome)** Median ARR decreased during tocilizumab treatment compared with before tocilizumab initiation, from 1.9 (range 0.1 to 6.3) to 0.1 (range 0 to 1.4) (p<0.0001, 95% CI 1.4 to 2.1). **Time to first relapse**	This study was appraised using the National Institutes for Health (NIH) quality assessment tool for before-after (pre-post) studies with no control group. 1. Yes 2. Yes 3. Yes, although some eligible people may have been excluded 4. Yes 5. Cannot determine 6. Yes and no – tocilizumab treatment has been clearly described but a

Study aim "This study evaluated the long-term effectiveness of tocilizumab for NMOSD." **Study dates** Study enrolment and follow up between October 2017 and January 2022	normal if they had previously received B-cell-targeted therapy • they had MOGAD or anti-glial fibrillary acidic protein encephalomyelitis • they had a history of clinically significant infection or heart, liver, kidney insufficiency • they had a current tumour disease or within the last 5 years. **Total sample size** N=65 No comparator group. **Baseline characteristics** Of the n=65 participants in the study: • 54 were AQP4-IgG positive NMOSD, 11 were AQP4-IgG negative NMOSD • 60 female, 5 male • the mean (SD) age at tocilizumab initiation was 48.3 years (±14.5 years) • the median disease duration was 4.1 years (IQR 2.9 to 5.3 years) • the median ARR before tocilizumab was 1.9 (IQR 0.1 to 6.3) • the median EDSS score was 5.5 (IQR 3.0 to 6.0) • 27 (41.5%) had a concomitant autoimmune disease • all had received corticosteroids prior to tocilizumab treatment. Other agents used prior to tocilizumab were IV immunoglobulin (35/65, 53.8%), mycophenolate (17/65, 26.1%), azathioprine (15/65, 23.1%), rituximab (12/65,	8 months), at which point tocilizumab was used as monotherapy. In 6/65 (9.2%) participants, all prior treatments were discontinued at the start of tocilizumab treatment and tocilizumab was used as monotherapy. **Comparators** No comparator.	The median time to first relapse was 15.5 (range 4 to 42) months. **Percentage relapse free** 50/65 (76.9%) participants were relapse free at the end of follow up. 10/65 (15.4%) participants had 1 attack; 5/65 (7.7%) participants had 2 attacks. Fourteen myelitis cases and 6 optic neuritis cases were reported after tocilizumab treatment. **Measure of disability** Between the start of tocilizumab and the end of the follow up period, 5/65 (7.7%) participants had worsening EDSS score. The EDSS score increased by less than 1 in acute attacks, indicating no severe relapse occurred during tocilizumab treatment. **Symptom alleviation** 34/65 (52%) participants experienced disease-related chronic pain before tocilizumab treatment, reporting a median pain intensity score of 2 (IQR 1.5 to 3.5) – this increased to 2.5 (IQR 1.5 to 4.0) after treatment. **Important outcomes** **Health related quality of life** Not reported **Hospitalisations / Hospital appointments** Not reported **Steroid reduction** Not reported **Safety** **AEs** 15/65 (23.1%) reported transient fatigue lasting a mean 3.4 (range 1 to 9) days. Infections occurred in 18/65 (27.7%), including urinary tract (n=11), upper respiratory tract (n=8), zoster virus (n=4), and pneumonia (n=3).	large variation in infusion intervals has been reported 7. No 8. No 9. Yes 10. Only for some outcomes 11. No 12. Not applicable Quality rating: Poor Other comments: The inclusion criteria are appropriate but the exclusion criteria regarding comorbidities and previous medication may have excluded some people who would be eligible in clinical practice. People under 18 years were excluded. The median ARR before tocilizumab has an IQR of 0.1 to 6.3, the lower range implies that some participants may not have been highly relapsing. Sample size appears to be opportunistic rather than predefined and no sample size calculations have been reported. Infusion intervals between 4 and 8 weeks are reported – infusion intervals greater than 4 weeks are due to a patient-oriented economic burden. Method of calculating ARR not reported. None of the investigators or treating physicians were blinded. Source of funding: 'The study was supported by the National Natural Science Foundation of China (grant no. 82171777) and the Natural Science Foundation of Tianjin Province (grant no. 20JCJQJC00280)'.

	18.5%) and cyclophosphamide (1/65, 1.5%) • participants had switched to tocilizumab mainly due to disease breakthrough or adverse events under prior immunosuppressants (figures not reported).		Infusion related reactions occurred in 5/65 (7.7%), including skin rash (n=2), lower limb oedema (n=2), headache (n=1), dizziness (n=1) and hypotension (n=1). 7/65 (10.7%) had hypercholesterolaemia. 28/65 (43%) had mild to moderate increases in serum alanine transaminase level. **Prespecified subgroups** Results were reported by AQP4-IgG status. **AQP4-IgG positive NMOSD** n=54, median follow up not reported for this subgroup. **Critical outcomes** **Relapse rate** Median ARR decreased in participants with AQP4-IgG positive NMOSD compared with before tocilizumab treatment, from 1.89 to 0.14 (p<0.0001, 95% CI 1.38 to 2.12). The median time to first relapse in participants with AQP4-IgG positive NMOSD was 18.6 months. 41/54 (75.9%) participants with AQP4-IgG positive NMOSD were relapse free at the end of follow up. **Measure of disability** Between the start of tocilizumab treatment and the end of the follow up period, 4/54 (7.4%) participants with AQP4-IgG positive NMOSD had worsening EDSS score. In participants with AQP4-IgG positive NMOSD, median EDSS score decreased from 5.75 (range 1 to 8.5) to 3.5 (range 0 to 8) (p<0.001). **AQP4-IgG negative NMOSD** n=11, median follow up not reported for this subgroup. **Critical outcomes** **Relapse rate** Median ARR decreased in participants with AQP4-IgG negative NMOSD compared with before the start of tocilizumab treatment from 1.75 to 0.06 (p<0.0001, 95% CI 1.22 to 2.49).	

			The median time to first relapse in participants with AQP4-IgG negative NMOSD was 15.5 months. 9/11 (81.8%) participants with AQP4-IgG negative NMOSD were relapse free at the end of follow up. **Measure of disability** Between the start of tocilizumab and the end of the follow up period, 1/11 (9.1%) participants with AQP4-IgG negative NMOSD had worsening EDSS score. In participants with AQP4-IgG negative NMOSD, median EDSS score decreased from 5 (range 1.5 to 6.0) to 2.5 (range 0 to 5.5) (p=0.043). **Direct comparisons of AQP4-IgG status** The median ARR after treatment did not differ between AQP4-IgG positive NMOSD and AQP4-IgG negative NMOSD groups (0.14 and 0.06 respectively, p=0.3618). The median time to first relapse did not differ between AQP4-IgG positive NMOSD and AQP4-IgG negative NMOSD groups (18.6 and 15.5 months respectively, p=0.7210). **Cost effectiveness** Not reported	
Full citation Zhang C, Zhang M, Qiu W et al. for the TANGO Study Investigators (2020) **Safety and efficacy of tocilizumab versus azathioprine in highly relapsing neuromyelitis optica spectrum disorder (TANGO): an open-label, multicentre, randomised, phase 2 trial.** Lancet Neurology. Vol 19, Issue 5, Pages 391-401, May. **Study location** Six hospitals in China. **Study type** Open-label, multicentre, randomised phase 2 trial.	**Inclusion criteria** Adults (aged ≥18 years) with highly relapsing NMOSD, who: • were diagnosed according to 2015 International diagnostic criteria for NMOSD • had an EDSS score of 7.5 or lower • a history of at least 2 clinical relapses during the previous 12 months, or 3 relapses in the previous 24 months, with at least 1 relapse in the previous 12 months. **Exclusion Criteria** People were excluded if:	**Interventions** Tocilizumab 8 mg/kg IV every 4 weeks. For infusion related reactions, adjustments to the infusion rate and prednisone or diphenhydramine were permitted. Concomitant immunosuppressants were permitted for the first 12 weeks, thereafter tocilizumab was used as monotherapy. **Comparators** Oral azathioprine, initially 25 mg, increased stepwise in 25 mg per day increments until a target dose of 2 to 3 mg/kg per day was reached.	The primary outcome of the TANGO trial was time to first relapse. Relapse was defined as new onset neurological symptoms or worsening of existing neurological symptoms with an objective change on neurological examination that persisted for more than 24 hours, with signs and symptoms attributable solely to NMOSD, and preceded by at least 30 days of clinical stability. MRI was used to confirm cases of relapse for which clinical changes on examination did not meet relapse criteria. A relapse required a change in the EDSS score regardless of MRI. **Critical outcomes** **Relapse rate** **Median time to first relapse (primary outcome)** Median time to first relapse in the full analysis set was longer in the tocilizumab group (78.9 [IQR 58.3 to 90.6] weeks) compared with the azathioprine group (56.7 [IQR 32.9 to 81.7] weeks) (p=0.0026).	This study was appraised using the Cochrane risk-of-bias tool for randomised trials. DOMAIN 1: Risk of bias arising from the randomization process 1.1 Yes (computer generated) 1.2 No (investigators and patients were aware of treatment allocation) 1.3 Probably no (there are some small differences in baseline characteristics, but it is unclear if the differences are significant as not formally assessed by the authors) Risk of bias judgement: high risk Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) 2.1 Yes (open-label study)

Study aim "To compare the safety and efficacy of tocilizumab and azathioprine in patients with highly relapsing NMOSD". **Study dates** Study enrolment was between 1 November 2017 and 3 August 2018.	• there was evidence of clinically significant infection • they were pregnant, or planning to conceive during the trial period • had previously relapsed on azathioprine • they had a heterozygous or homozygous thiopurine methyltransferase gene mutation • had received rituximab or any experimental β-cell-depleting drug in the previous 6 months • presented with >1% CD19-positive B cells in peripheral blood mononuclear cells. **Total sample size** N=118, randomised 1:1 to receive tocilizumab or azathioprine. **No. of participants in each treatment group** The study comprised a full analysis set in which 59 participants were randomised to tocilizumab and 59 to azathioprine (n=118), and a per protocol analysis which included 56 participants randomised to tocilizumab and 52 to azathioprine who were adherent to monotherapy treatment. **Baseline characteristics** The authors reported that the baseline characteristics were generally balanced, however, no analysis was reported. Of the n=118 participants in the study: • 50 (85%) of the tocilizumab and 53 (90%) of the	For medication related symptoms during the loading period symptomatic treatments were allowed (apart from new immunosuppressants). Concomitant immunosuppressants were permitted for those randomised to azathioprine during the first 24 weeks: • those without previous azathioprine treatment received 24 weeks of concomitant treatment • those who had less than 24 weeks of azathioprine treatment previously received concomitant immunosuppressants until they had received 24 weeks of azathioprine treatment • those who had previously had azathioprine for longer than 24 weeks received no concomitant immunosuppressants. After 24 weeks azathioprine was used as monotherapy. The study had a minimum follow up period of 60 weeks, with a stopping criterion of at least 30 relapses. Participants reached the end of the study when they relapsed, or when the last enrolled participant completed their last scheduled visit.	**Risk of relapse** At 60 weeks risk of relapse was significantly lower in the tocilizumab group compared with the azathioprine group (HR 0.274, 95% CI 0.123 to 0.607, p=0.0006). At the end of the study[3], in the full analysis set 36 relapses occurred during the study, 8/59 (14%) occurred in the tocilizumab group compared with 28/59 (47%) in the azathioprine group (HR 0.236, 95% CI 0.107 to 0.518, p<0.0001). **Percentage relapse free** At the end of the study[3], the proportion of those who were relapse free in the per protocol analysis was 50/56 (89%) in the tocilizumab group and 29/52 (56%) in the azathioprine group (HR 0.188, 95% CI 0.076 to 0.463, p<0.0001). **Measure of disability[4]** Confirmed disability progression at 12 weeks in the full analysis set was significantly lower in the tocilizumab group (5/59, 8%) compared with (15/59, 25%) in the azathioprine group (HR 0.288, 95% CI 0.105 to 0.795, p=0.0087). An exploratory outcome of the study was confirmed disability progression at 24 weeks in the full analysis set which was lower in the tocilizumab group (2/59, 3%) compared with (6/59, 10%) in the azathioprine group (HR 0.221, 95% CI 0.047 to 1.042, p=0.0309). Between baseline and end of study[3], more participants in the azathioprine group compared with the tocilizumab group had worsening of EDSS score (RR 3.667, 95% CI 1.603 to 8.387; p=0.0005). However, the mean (SD) change of EDSS score (−0.32 ± 0.72 in tocilizumab compared with −0.13 ± 1.05 in the azathioprine) was reported as not significantly different (−0.20, 95% CI −0.52 to −0.13; p=0.242). **Eye symptoms** For eye symptoms, monocular visual function was assessed, and the study separated the eyes by affected and unaffected. **Optic neuritis** Participants in the tocilizumab group (1 attack in affected eyes and no attacks in unaffected eyes) had a lower risk of optic neuritis than those in the azathioprine group (3 attacks in affected eyes and 6 attacks in unaffected eyes), HR 0.182, 95% CI 0.049 to 0.677; p=0.011. No follow up time reported.	2.2 Yes (open-label study) 2.3 Probably no 2.4 Not applicable 2.5 Not applicable 2.6 Yes (a full analysis set [ITT] and per protocol analyses were conducted) 2.7 Not applicable Risk of bias judgement: low risk Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) 2.1 Yes (open-label study) 2.2 Yes (open-label study) 2.3 Not applicable 2.4 Probably no 2.5 Probably no 2.6 Not applicable Risk of bias judgement: low risk Domain 3: Missing outcome data 3.1 Yes (only 5 participants were lost to follow up in the trial, 2 deaths and 3 withdrew due to SAE) 3.2 Probably yes 3.3 Probably no 3.4 Probably no Risk of bias judgement: low risk Domain 4: Risk of bias in measurement of the outcome 4.1 No (validated and objective outcomes)

	azathioprine participants were AQP4-IgG positive • 108 (92%) were female • the mean (SD) age was 48.1 (±13.4) and 45.3 (±14.5) years in the tocilizumab and azathioprine groups, respectively • the mean (SD) disease history was 6.0 (±2.9) and 6.2 (±3.1) years in the tocilizumab and azathioprine groups, respectively • the mean (SD) annualised relapse rate (ARR) during the previous 24 months was 1.69 (±0.64) • the median EDSS score was 4.5 (IQR 4.0 to 5.5) • 47 (40%) had concomitant autoimmune disease • immunosuppressant therapy at baseline was similar with 39% in both the tocilizumab and azathioprine groups being treated with monotherapy[1] and 58% and 61% in the azathioprine and tocilizumab groups being on dual therapy[2]. An additional 1 participant was on IVIG monotherapy, and 1 other was on no treatment, both in the tocilizumab group.		NB optic neuritis was also one of the criteria that was used to define relapse in NMOSD. **Visual acuity** There was no significant difference in the mean rate of change per month in LogMAR visual acuity between the tocilizumab and azathioprine groups in either affected (MD −0.0095, 95% CI −0.0191 to 0.0002; p=0.0558) or unaffected eyes (MD 0.0012, 95% CI −0.0032 to 0.0056; p=0.5796) measured between baseline and 60 weeks. There was no significant difference in the exploratory outcome of mean rate of change per month in high-contrast letter score (100%) between the tocilizumab and azathioprine groups in either affected (MD 0.3553, 95% CI −0.0833 to 0.7938; p=0.1110) or unaffected eyes (MD 0.0034, 95% CI −0.0300 to 0.0367; p=0.8398) measured between baseline and 60 weeks. There was no significant difference in the exploratory outcome of mean rate of change per month in low-contrast letter score (2.5%) between the tocilizumab and azathioprine groups in either affected (MD 0.1113, 95% CI −0.0078 to 0.2304; p=0.0667) or unaffected eyes (MD 0.0164, 95% CI 0.0292 to 0.1415; p=0.4190) measured between baseline and 60 weeks. **Symptom alleviation** Not reported **Important outcomes** **Health related quality of life** Not reported **Hospitalisations / Hospital appointments** Not reported **Steroid reduction** Not reported **Safety** **AEs** Incidence of AEs was similar between the tocilizumab (57/59, 97%) and azathioprine (56/59, 95%) groups and most were described as mild. Most commonly these were increased alanine transaminase concentrations (18/59, 31% in the tocilizumab group compared with 27/59, 46% in the azathioprine group), upper respiratory	4.2 No (outcome assessors were blinded to treatment allocation using objective definitions of outcomes) 4.3 No 4.4 Not applicable 4.5 Not applicable Risk of bias judgement: low risk Domain 5: Risk of bias in selection of the reported result 5.1 Yes 5.2 No 5.3 No Risk of bias judgement: low risk Overall risk of bias judgement: **some concerns** Other comments: The main risk of bias in the trial is from the open-label (participants and investigators aware of assignment) nature of the trial. However, only small differences were seen in baseline characteristics and outcomes were assessed centrally, and laboratory personnel and radiologists were all masked to treatment assignment. The other domains were assessed as at low risk. Source of funding: The study was funded by the Tianjin Medical University Clinical Research Project (2017kylc005), the Advanced Innovation Center for Human Brain Protection (Neuroimmune01), the National Key Research and Development Program of China (2018YFC1312200) and the National Science Foundation of China (91642205, 81830038, and 81601019). The authors report that the study funders had no role in study design, data collection, data analysis, data interpretation or the writing of the report.

			tract infection (17/59, 29% in the tocilizumab group compared with 23/59, 39% in the azathioprine group) and urinary tract infections (17/59, 29% in the tocilizumab group compared with 21/59, 36% in the azathioprine group). **Grade 3 and 4 AEs** Grade 3 (severe) and grade 4 (life-threatening) adverse events were higher in the azathioprine group (21/59, 36%) than in the tocilizumab group (9/59, 15%). **AEs leading to discontinuation** Of the AEs (1/59, 2%) in the tocilizumab group and (2/59, 3%) in the azathioprine group led to discontinuation of a study drug. **SAEs (not a prespecified outcome)** Incidence of SAEs was higher in the azathioprine group (9/59, 15%) than in the tocilizumab group (5/59, 8%). **Mortality (not a prespecified outcome)** Two deaths (1 in each of the tocilizumab and azathioprine groups) occurred during the study, neither was considered treatment related. In the azathioprine group the death was caused by severe intracranial infection and cerebral oedema. In the tocilizumab group the death was central respiratory failure secondary to myelitis. **Cost effectiveness** Not reported **Prespecified subgroups** Several prespecified subgroup analyses of the primary outcome (time to first relapse) were conducted including AQP4-IgG status. In participants who were AQP4-IgG positive, the relapse risk was significantly lower in the tocilizumab group (6/50, 12%) compared with the azathioprine group (25/53, 47%), HR 0.202, 95% CI 0.083 to 0.493; p=0.0004 at the end of the study[3]. In participants who were AQP4-IgG negative, there was no significant difference in relapse risk between those in the tocilizumab group (2/9, 22%) compared with the azathioprine group (3/6, 50%), HR 0.470, 95% CI 0.078 to 2.821, p=0.408) at the end of the study[3]. Of the AQP4-IgG seronegative group, n=3 were participants who had MOGAD (1 in the tocilizumab and 2 in the azathioprine groups). The participant in the tocilizumab group	

			was relapse free at the end of the study, of the 2 participants in the azathioprine group 1 was relapse free at the end of the study[3] and the other had a single relapse (at day 580).	

1. Single therapy was oral corticosteroids, mycophenolate mofetil, azathioprine, tacrolimus, cyclophosphamide or methotrexate.

2. Combined therapy was oral corticosteroids and azathioprine, oral corticosteroids and mycophenolate mofetil, oral corticosteroids and methotrexate, oral corticosteroids and cyclophosphamide, oral corticosteroids and tacrolimus, azathioprine and cyclophosphamide, oral corticosteroids and cyclosporin, or oral corticosteroids and IVIG.

3. Some participants were followed up for 90 weeks; 43/59 (73%) in the tocilizumab group and 25/59 (42%) in the azathioprine group. This was not a trial amendment but due to the length of time required to recruit to required sample size.

4. Disability progression was an increase in EDSS score of at least 1.0 point from baseline, sustained for at least 12 weeks (or 24 weeks for the exploratory outcome) if the baseline EDSS score was 5.5 or less, or an increase in EDSS score of at least 0.5 points from baseline, sustained for at least 12 weeks (or 24 weeks) if the baseline EDSS score was greater than 5.5.

Abbreviations

ADEM, acute disseminated encephalomyelitis; AE, adverse event; ARR, annualised relapse rate; AQP4-IgG, aquaporin-4 immunoglobulin G; CNS, central nervous system; CI, confidence interval; EDSS, Expanded Disability Status Scale; IQR, interquartile range; ITT, intention to treat; HR, hazard ratio; IVIG, intravenous immunoglobulin; IV, intravenous; LogMAR, Logarithm of the Minimum Angle of Resolution; mg/kg, milligrams per kilogram; MD, mean difference; MRI, magnetic resonance imaging; MOG, myelin oligodendrocyte glycoprotein; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; OR, odds ratio; RR, relative risk; SAE, serious adverse event; SC, subcutaneous; SD, standard deviation.

Appendix F Quality appraisal checklists

The National Institutes of Health (NIH) quality assessment tool for before-after (pre-post) study with no (concurrent) control group

1. Was the study question or objective clearly stated?

2. Were eligibility/selection criteria for the study population prespecified and clearly described?

3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?

4. Were all eligible participants that met the prespecified entry criteria enrolled?

5. Was the sample size sufficiently large to provide confidence in the findings?

6. Was the test/service/intervention clearly described and delivered consistently across the study population?

7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?

8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?

9. Was the loss to follow up after baseline 20% or less? Were those lost to follow up accounted for in the analysis?

10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?

11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?

12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Cochrane risk-of-bias tool for randomized trials checklist

Domain 1: Risk of bias arising from the randomization process	
1.1 Was the allocation sequence random?	
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	
Risk-of-bias judgement	Low / High / Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	

2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	
Risk-of-bias judgement	Low / High / Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	
Risk-of-bias judgement	Low / High / Some concerns
Domain 3: Missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	
Risk-of-bias judgement	Low / High / Some concerns
Domain 4: Risk of bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	
Risk-of-bias judgement	Low / High / Some concerns
Domain 5: Risk of bias in selection of the reported result	

5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...	
5.2.... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	
5.3... multiple eligible analyses of the data?	
Risk-of-bias judgement	Low / High / Some concerns
Overall risk-of-bias judgement	Low / High / Some concerns

Appendix G GRADE profiles

Question 1: In patients with neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) who are intolerant to or whose disease is refractory to previous lines of therapy, what is the clinical effectiveness of tocilizumab compared with current standard of care or best supportive care?

Table 2: Relapse rate: tocilizumab compared with azathioprine in NMOSD or MOGAD

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Tocilizumab	Azathioprine	Result (95%CI)		
Relapse rate (1 open-label randomised trial)									
Risk of relapse at 60 weeks									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	No serious	n=59	n=59	Lower in the tocilizumab group compared with the azathioprine group: HR 0.274 (95% CI 0.123 to 0.607; p=0.0006).	Critical	Moderate
Risk of relapse at the end of the study (up to 90 weeks)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	No serious	8/59 (14%)	28/59 (47%)	Lower in the tocilizumab group compared with the azathioprine group: HR 0.236 (95% CI 0.107 to 0.518; p<0.0001).	Critical	Moderate
Percentage relapse free at the end of the study (up to 90 weeks)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	No serious	50/56 (89%)	29/52 (56%)	Higher in the tocilizumab group compared with the azathioprine group: HR 0.188 (95% CI 0.076 to 0.463; p<0.0001). Per protocol analysis[a]	Critical	Moderate
Median time to first relapse (primary outcome)									

One open label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	Not calculable	n=59 78.9 (IQR 58.3 to 90.6) weeks	n=59 56.7 (IQR 32.9 to 81.7) weeks	Longer in the tocilizumab group compared with the azathioprine group: (p=0.0026).	Critical	Moderate

Abbreviations

CI, confidence interval; IQR, interquartile range; HR, hazard ratio.

1 Downgraded 1 level – people were excluded if they had previously relapsed on azathioprine or had received rituximab in the previous 6 months. Participants in the tocilizumab group were permitted concomitant immunosuppressants for the first 12 weeks.

a The per protocol population included all participants who used azathioprine or tocilizumab as monotherapy.

Table 3: Relapse rate: no comparator in NMOSD or MOGAD

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Tocilizumab**	**No comparator**	**Result (95%CI)**		
Relapse rate (2 observational retrospective studies)									
Percentage relapse free after median duration of 23.8 (IQR 13.0 to 51.1) months tocilizumab treatment									
One retrospective observational study Ringelstein et al. 2022	Serious[1]	Serious[2]	Not applicable	Not calculable	34/57 (60%)	–		Critical	Very low
Percentage relapse free after median duration of 34.1 (IQR 25.5 to 39.3) months tocilizumab treatment									
One retrospective observational study Yang et al. 2023	Serious[3]	Serious[4]	Not applicable	Not calculable	50/65 (76.9%)	–	10/65 (15.4%) participants had 1 attack; 5/65 (7.7%) participants had 2 attacks. Fourteen myelitis cases and 6 optic neuritis cases were reported after tocilizumab treatment.	Critical	Very low
Median time to first relapse									
One retrospective	Serious[1]	Serious[2]	Not applicable	Not calculable	n=57	–	9 months (range 0.5 to 47 months).	Critical	Very low

observational study Ringelstein et al. 2022									
One retrospective observational study Yang et al. 2023	Serious[3]	Serious[4]	Not applicable	Not calculable	n=65	–	15.5 months (range 4 to 42 months).	Critical	Very low
Median ARR over a median duration of 23.8 (IQR 13.0 to 51.1) months tocilizumab treatment (primary outcome)									
One retrospective observational study Ringelstein et al. 2022	Serious[1]	Serious[2]	Not applicable	Not calculable	n=57	–	0 compared with 1.5 in the 2-year baseline period prior to tocilizumab treatment (p<0.001, 95% CI 1.1 to 1.8).	Critical	Very low
Median ARR over a median duration of 34.1 (IQR 25.5 to 39.3) months tocilizumab treatment (primary outcome)									
One retrospective observational study Yang et al. 2023	Serious[3]	Serious[4]	Not applicable	Not calculable	n=65	–	0.1 (range 0 to 1.4) compared with 1.9 (range 0.1 to 6.3) before tocilizumab treatment (p<0.0001, 95% CI 1.4 to 2.1).	Critical	Very low

Abbreviations

ARR, annualised relapse rate; CI, confidence interval; IQR, interquartile range.

1 Downgraded 1 level – quality assessment raised some concerns such as: lack of blinding; how eligibility was defined and whether all eligible people were included; and uncertainty around whether analysis decisions were made before data collection.
2 Downgraded 1 level – no comparator arm. 18% of participants were given tocilizumab alongside other immunosuppressants (excluding corticosteroids). People with acute disseminated encephalomyelitis were excluded although this is a recognised manifestation of MOGAD. The bottom range of median ARR before tocilizumab was between 0 and 1 for all population subgroups, indicating that some participants may not have been highly relapsing.
3 Downgraded 1 level – quality assessment raised some concerns, including lack of blinding, unclear methods for calculating ARR and uncertainty whether analysis decisions were made before data collection.
4 Downgraded 1 level – no comparator arm. People were excluded if they had received immunosuppressants within the expected pharmacodynamic effect window prior to initiation of tocilizumab, such as azathioprine or rituximab within 6 months. The IQR of median ARR before tocilizumab was 0.1 to 6.3, indicating that some participants may not have been highly relapsing. Infusion intervals varied, between 4 and 8 weeks.

Table 4: Measure of disability: tocilizumab compared with azathioprine in NMOSD or MOGAD

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Tocilizumab	Azathioprine	Result (95%CI)		
Measure of disability (1 open-label randomised trial)									
Number of participants with confirmed disease progression at 12 weeks[A]									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	No serious	5/59 (8%)	15/59 (25%)	Lower in the tocilizumab group compared with the azathioprine group: HR 0.288 (95% CI 0.105 to 0.795, p=0.0087).	Critical	Moderate
Number of participants with confirmed disease progression at 24 weeks[A] (exploratory outcome)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	Serious	2/59 (3%)	6/59 (10%)	Lower in the tocilizumab group compared with the azathioprine group: HR 0.221 (95% CI 0.047 to 1.042, p=0.0309).[a]	Critical	Low
Mean change in EDSS[B] score at the end of the study (up to 90 weeks) (higher scores represent higher levels of disability)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	No serious	n=59 −0.32 (SD ±0.72)	n=59 −0.13 (SD ±1.05)	No difference between the tocilizumab group and the azathioprine group: MD −0.20 (95% CI −0.52 to −0.13; p=0.242).[a]	Critical	Moderate
Number of participants with a worsening EDSS[B] score at the end of the study (up to 90 weeks)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	No serious	n=59	n=59	More participants in the azathioprine group had worsening of EDSS score compared with the tocilizumab group: RR 3.667 (95% CI 1.603 to 8.387; p=0.0005).	Critical	Moderate
Mean rate of change per month between baseline and 60 weeks in LogMAR visual acuity in affected eyes (a decrease in score represents recovery of vision)									
One open-label	No serious	Serious[1]	Not applicable	No serious	n=59	n=59	No difference between the tocilizumab group and the azathioprine group: MD	Critical	Moderate

randomised trial Zhang et al. 2020					0.0022 (SD ±0.0084)	0.0117 (SD ±0.0418)	−0.0095 (95% CI −0.0191 to 0.0002; p=0.0558).		
Mean rate of change per month between baseline and 60 weeks in LogMAR visual acuity in unaffected eyes (a decrease in score represents recovery of vision)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	No serious	n=59 −0.0002 (SD ±0.0019)	n=59 −0.0014 (SD ±0.0135)	No difference between the tocilizumab group and the azathioprine group: MD 0.0012 (95% CI −0.0032 to 0.0056; p=0.5796).	Critical	Moderate
Mean rate of change per month between baseline and 60 weeks in high-contrast letter score in affected eyes (an increase in score represents recovery of vision) (exploratory outcome)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	No serious	n=59 −0.0874 (SD ±0.3886)	n=59 −0.4426 (SD ±1.8910)	No difference between the tocilizumab group and the azathioprine group: MD 0.3553 (95% CI −0.0833 to 0.7938; p=0.1110).	Critical	Moderate
Mean rate of change per month between baseline and 60 weeks in high-contrast letter score in unaffected eyes (an increase in score represents recovery of vision) (exploratory outcome)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	Very serious	n=59 0.0043 (SD ±0.0126)	n=59 0.0009 (SD ±0.0103)	No difference between the tocilizumab group and the azathioprine group: MD 0.0034 (95% CI −0.0300 to 0.0367; p=0.8398).	Critical	Very low
Mean rate of change per month between baseline and 60 weeks in low-contrast letter score in affected eyes (an increase in score represents recovery of vision) (exploratory outcome)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	Serious	n=59 −0.0361 (SD ±0.2473)	n=59 −0.1473 (SD ±0.4574)	No difference between the tocilizumab group and the azathioprine group: MD 0.1113 (95% CI −0.0078 to 0.2304; p=0.0667).	Critical	Low
Mean rate of change per month between baseline and 60 weeks in low-contrast letter score in unaffected eyes (an increase in score represents recovery of vision) (exploratory outcome)									
One open-label	No serious	Serious[1]	Not applicable	Not calculable	n=59	n=59	No difference between the tocilizumab group and the azathioprine group: MD	Critical	Moderate

randomised trial Zhang et al. 2020					−0.0082 (SD ±0.0153)	−0.0246 (SD ±0.0120)	0.0164 (95% CI 0.0292 to 0.1415; p=0.4190).[b]		
Risk of optic neuritis attack (no timepoint reported) (NB optic neuritis was also one of the criteria that was used to define relapse in NMOSD)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	No serious	n=59 One attack in affected eyes, no attacks in unaffected eyes	n=59 Three attacks in affected eyes and 6 attacks in unaffected eyes	Lower in the tocilizumab group compared with the azathioprine group: HR 0.182 (95% CI 0.049 to 0.677; p=0.011).	Critical	Moderate

Abbreviations

CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; LogMAR, Logarithm of the Minimum Angle of Resolution; MD, mean difference; RR, relative risk; SD, standard deviation.

A Disability progression was defined as an increase in Expanded Disability Status Scale (EDSS) score of at least 1.0 point from baseline that was sustained on subsequent visits for at least 12 or 24 weeks if the baseline EDSS score was 5.5 or less, or an increase in the EDSS score of at least 0.5 points that was sustained for at least 12 or 24 weeks if the baseline score was greater than 5.5. Participants with initial disability progression during the treatment period who discontinued treatment early and did not have a subsequent visit with confirmatory measurement of EDSS score were considered to have confirmed disability progression.
B The EDSS is a method of assessing an individual's level of disability and was developed for use in multiple sclerosis. It ranges from 0 (a normal neurological exam) to 10 (death due to multiple sclerosis). Points 1.0 to 4.5 on the scale measure impairment in following functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and other. Points 5.0 to 9.5 assess mobility impairment. A score up to 5 represents normal walking ability with some functional system impairment. A score above 5 represents impairment in mobility.

1 Downgraded 1 level – people were excluded if they had previously relapsed on azathioprine or had received rituximab in the previous 6 months. Participants in the tocilizumab group were permitted concomitant immunosuppressants for the first 12 weeks.

a Inconsistency noted between reported p value and confidence intervals.
b Mean difference point estimate not within reported confidence intervals, unable to calculate imprecision.

Table 5: Measure of disability: no comparator in NMOSD or MOGAD

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Tocilizumab	No comparator	Result (95%CI)		
Measure of disability (2 retrospective observational studies)									
Median EDSS[A] score at last follow up during a median duration of 23.8 (IQR 13.0 to 51.1) months tocilizumab treatment (higher scores represent higher levels of disability)									
One retrospective observational study Ringelstein et al. 2022	Serious[1]	Serious[2]	Not applicable	Not calculable	n=57	–	3.5 (IQR 2.0 to 6.5) compared with 4.5 (IQR 3.0 to 7.0) at start of tocilizumab treatment. No statistical analyses reported.	Critical	Very low
Number of participants with a worsening EDSS[A] score at last follow up during a median duration of 23.8 (IQR 13.0 to 51.1) months tocilizumab treatment									
One retrospective observational study Ringelstein et al. 2022	Serious[1]	Serious[2]	Not applicable	Not calculable	5/57 (9%)	–		Critical	Very low
Number of participants with a worsening EDSS[A] score after a median duration of 34.1 (IQR 25.5 to 39.3) months tocilizumab treatment									
One retrospective observational study Yang et al. 2023	Serious[3]	Serious[4]	Not applicable	Not calculable	5/65 (7.7%)	–	The EDSS score increased by less than 1 in acute attacks, indicating no severe relapse occurred during tocilizumab treatment.	Critical	Very low

Abbreviations

EDSS, Expanded Disability Status Scale; IQR, interquartile range.

A The Expanded Disability Status Scale (EDSS) is a method of assessing an individual's level of disability and was developed for use in multiple sclerosis. It ranges from 0 (a normal neurological exam) to 10 (death due to multiple sclerosis). Points 1.0 to 4.5 on the scale measure impairment in following functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and other. Points 5.0 to 9.5 assess mobility impairment. A score up to 5 represents normal walking ability with some functional system impairment. A score above 5 represents impairment in mobility.

1 Downgraded 1 level – quality assessment raised some concerns such as: lack of blinding; how eligibility was defined and whether all eligible people were included; and uncertainty around whether analysis decisions were made before data collection. p values not reported for outcomes.

2 Downgraded 1 level – no comparator arm. 18% of participants were given tocilizumab alongside other immunosuppressants (excluding corticosteroids). People with acute disseminated encephalomyelitis were excluded although this is a recognised manifestation of MOGAD. The bottom range of median ARR before tocilizumab was between 0 and 1 for all population subgroups, indicating that some participants may not have been highly relapsing.
3 Downgraded 1 level – quality assessment raised some concerns, including lack of blinding and uncertainty whether analysis decisions were made before data collection.
4 Downgraded 1 level – no comparator arm. People were excluded if they had received immunosuppressants within the expected pharmacodynamic effect window prior to initiation of tocilizumab, such as azathioprine or rituximab within 6 months. The IQR of median ARR before tocilizumab was 0.1 to 6.3, indicating that some participants may not have been highly relapsing. Infusion intervals varied, between 4 and 8 weeks.

Table 6: Symptom alleviation: no comparator in NMOSD or MOGAD

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Tocilizumab**	**No comparator**	**Result (95%CI)**		
Symptom alleviation (2 retrospective observational studies)									
Median chronic pain occurrence and intensity scores at last follow up during up to a median duration of 23.8 (IQR 13.0 to 51.5) months tocilizumab treatment (mild = 1, moderate = 2, severe = 3)									
One retrospective observational study Ringelstein et al. 2022	Serious[1]	Serious[2]	Not applicable	Not calculable	n=52	–	2.0 (IQR 1 to 3) (25/52 reported ongoing chronic pain, score data from 24 participants), compared with 2.0 (IQR 1 to 3) at baseline (28/51 reported chronic pain at baseline, score data from 27 participants). No statistical analyses reported.	Critical	Very low
Median NMOSD-related pain intensity scores after a median duration of 34.1 (IQR 25.5 to 39.3) months tocilizumab treatment (scale 0 (no pain) to 10 (worst pain imaginable))									
One retrospective observational study Yang et al. 2023	Serious[3]	Serious[4]	Not applicable	Not calculable	n=34	–	2.5 (IQR 1.5 to 4.0) compared with 2 (IQR 1.5 to 3.5) at baseline. No statistical analyses reported.	Critical	Very low

Abbreviations

IQR, interquartile range.

1 Downgraded 1 level – quality assessment raised some concerns such as: lack of blinding; how eligibility was defined and whether all eligible people were included; and uncertainty around whether analysis decisions were made before data collection. p values not provided for outcomes. Unclear if tool used for assessing pain is validated.
2 Downgraded 1 level – no comparator arm. In 18% of participants, tocilizumab was given alongside other immunosuppressants (excluding corticosteroids). People with acute disseminated encephalomyelitis were excluded although this is a recognised manifestation of MOGAD. The bottom range of median ARR before tocilizumab was between 0 and 1 for all population subgroups, indicating that some participants may not have been highly relapsing.
3 Downgraded 1 level – quality assessment raised some concerns, including lack of blinding and uncertainty whether analysis decisions were made before data collection. p values not provided for outcomes.

4 Downgraded 1 level – no comparator arm. People were excluded if they had received immunosuppressants within the expected pharmacodynamic effect window prior to initiation of tocilizumab, such as azathioprine or rituximab within 6 months. The IQR of median ARR before tocilizumab was 0.1 to 6.3, indicating that some participants may not have been highly relapsing. Infusion intervals varied, between 4 and 8 weeks.

Table 7: Safety: tocilizumab compared with azathioprine in NMOSD or MOGAD

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Tocilizumab**	**Azathioprine**	**Result (95%CI)**		
Safety (1 open-label randomised trial)									
Number of participants who experienced adverse events during the study (up to 90 weeks)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	Not calculable	57/59 (97%)	56/59 (95%)	Most were described as mild. Most commonly these were increased alanine transaminase concentrations (18/59, 31% in the tocilizumab group compared with 27/59, 46% in the azathioprine group), upper respiratory tract infection (17/59, 29% in the tocilizumab group compared with 23/59, 39% in the azathioprine group) and urinary tract infections (17/59, 29% in the tocilizumab group compared with 21/59, 36% in the azathioprine group). No statistical analyses reported.	Important	Moderate
Number of participants who experienced grade 3 (severe) or grade 4 (life-threatening) adverse events during the study (up to 90 weeks)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	Not calculable	9/59 (15%)	21/59 (36%)	No statistical analyses reported.	Important	Moderate
Number of participants who experienced serious adverse events during the study (up to 90 weeks)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	Not calculable	5/59 (8%)	9/59 (15%)	No statistical analyses reported.	Important	Moderate
Number of participants who discontinued treatment due to adverse events during the study (up to 90 weeks)									

One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	Not calculable	1/59 (2%)	2/59 (3%)	No statistical analyses reported.	Important	Moderate
Number of participants who died during the study (up to 90 weeks)									
One open-label randomised trial Zhang et al. 2020	No serious	Serious[1]	Not applicable	Not calculable	1/59 (2%)	1/59 (2%)	Neither death was considered treatment related. In the azathioprine group the death was caused by severe intracranial infection and cerebral oedema. In the tocilizumab group the death was central respiratory failure secondary to myelitis. No statistical analyses reported.	Important	Moderate

1 Downgraded 1 level – people were excluded if they had previously relapsed on azathioprine or had received rituximab in the previous 6 months. Participants in the tocilizumab group were permitted concomitant immunosuppressants for the first 12 weeks.

Table 8: Safety: no comparator in NMOSD or MOGAD

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Tocilizumab**	**No comparator**	**Result (95%CI)**		
Safety (2 retrospective observational studies)									
Adverse events experienced by at least 10% of participants during a median duration of 23.8 (IQR 13.0 to 51.1) months tocilizumab treatment									
One retrospective observational study Ringelstein et al. 2022	Serious[1]	Serious[2]	Not applicable	Not calculable	n=57	–	Infusion related reactions (7/57, 12%); recurrent urinary tract infections (9/57, 16%); upper respiratory tract infections, colds, bronchitis or pneumonia (9/57, 16%); neutropenia (10/57, 17%); transient and mild to moderate liver enzyme change (20/57, 35%).	Important	Very low
Adverse events experienced by participants during a median duration of 34.1 (IQR 25.5 to 39.3) months tocilizumab treatment									
One retrospective observational study	Serious[3]	Serious[4]	Not applicable	Not calculable	n=65	–	Transient fatigue (15/65, 23.1%) lasting a mean 3.4 days (range 1 to 9 days); infections (18/65, 27.7%) (including urinary tract (n=11), upper respiratory tract (n=8), zoster virus (n=4), and pneumonia (n=3)); infusion related reactions (5/65, 7.7%) (including skin	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Tocilizumab**	**No comparator**	**Result (95%CI)**		
Yang et al. 2023							rash (n=2), lower limb oedema (n=2), headache (n=1), dizziness (n=1) and hypotension (n=1)); hypercholesterolaemia (7/65, 10.7%); mild to moderate increases in serum alanine transaminase levels (28/65, 43%).		
Number of participants who discontinued treatment due to adverse events during a median duration of 23.8 (IQR 13.0 to 51.1) months tocilizumab treatment									
One retrospective observational study Ringelstein et al. 2022	Serious[1]	Serious[2]	Not applicable	Not calculable	5/57 (9%)	–		Important	Very low
Number of participants who died during a median duration of 23.8 (IQR 13.0 to 51.1) months tocilizumab treatment									
One retrospective observational study Ringelstein et al. 2022	No serious	Serious[2]	Not applicable	Not calculable	1/57 (2%)	–	Due to recurrent pneumonia. Occurred 2 months after discontinuation of a 6-month tocilizumab treatment period and considered unrelated to tocilizumab treatment by the physician.	Important	Very low

Abbreviations

IQR, interquartile range.

1 Downgraded 1 level – quality assessment raised some concerns such as: lack of blinding; how eligibility was defined and whether all eligible people were included; and uncertainty around whether analysis decisions were made before data collection.
2 Downgraded 1 level – no comparator arm. In 18% of participants, tocilizumab was given alongside other immunosuppressants (excluding corticosteroids). People with acute disseminated encephalomyelitis were excluded although this is a recognised manifestation of MOGAD. The bottom range of median ARR before tocilizumab was between 0 and 1 for all population subgroups, indicating that some participants may not have been highly relapsing.
3 Downgraded 1 level – quality assessment raised some concerns, including lack of blinding, unclear methods for calculating ARR and uncertainty whether analysis decisions were made before data collection.
4 Downgraded 1 level – no comparator arm. People were excluded if they had received immunosuppressants within the expected pharmacodynamic effect window prior to initiation of tocilizumab, such as azathioprine or rituximab within 6 months. The IQR of median ARR before tocilizumab was 0.1 to 6.3, indicating that some participants may not have been highly relapsing. Infusion intervals varied, between 4 and 8 weeks.

Glossary

Expanded Disability Status Scale (EDSS)	A measure of disability developed for use in multiple sclerosis and used in all the included studies. Scale ranges from 0 to 10; 0 is normal and 10 is death due to multiple sclerosis. Points 1.0 to 4.5 on the scale measure impairment in the following functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and other. Points 5.0 to 9.5 assess mobility impairment. A score up to 5 represents normal walking ability with some functional system impairment. A score above 5 represents impairment in mobility.

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