CO189

Comparative Efficacy of Voclosporin in Combination with Mycophenolate Mofetil versus Other Treatments in Active Lupus Nephritis: Systematic Review and Network Meta-Analysis

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BACKGROUND

- Lupus nephritis (LN) is a severe renal manifestation of systemic lupus erythematosus (SLE), affecting approximately 40% to 60% of those who have SLE. Until 2021 when belimumab was licensed for the treatment of active LN in Europe, clinical practice has historically focused on off-label treatments. EULAR/ERA-EDTA recommendations (2019) include mycophenolate mofetil (MMF), cyclophosphamide (CYC), azathioprine (AZA) and glucocorticoids, with a calcineurin inhibitor (CNI) or rituximab (RTX) used as first line treatments for active LN in some circumstances.
- Voclosporin (VCS) received marketing authorisation from the European Medicines Agency (EMA) on 15 September 2022 and is the first licensed CNI for LN in Europe. In the pivotal Phase III clinical trial (AURORA 1, NCT03021499), VCS+MMF with a low-dose steroid regimen (2.5mg/day by week 16) demonstrated a significantly improved complete renal response (CR) rate and a significant reduction in median time to urine protein/creatinine ratio (UPCR) ≤ 0.5 mg/mg compared to MMF and low-dose steroids alone.

OBJECTIVES

- The objective is to determine the comparative effectiveness of VCS+MMF versus other therapies for achieving CR in patients with active LN.

METHODS

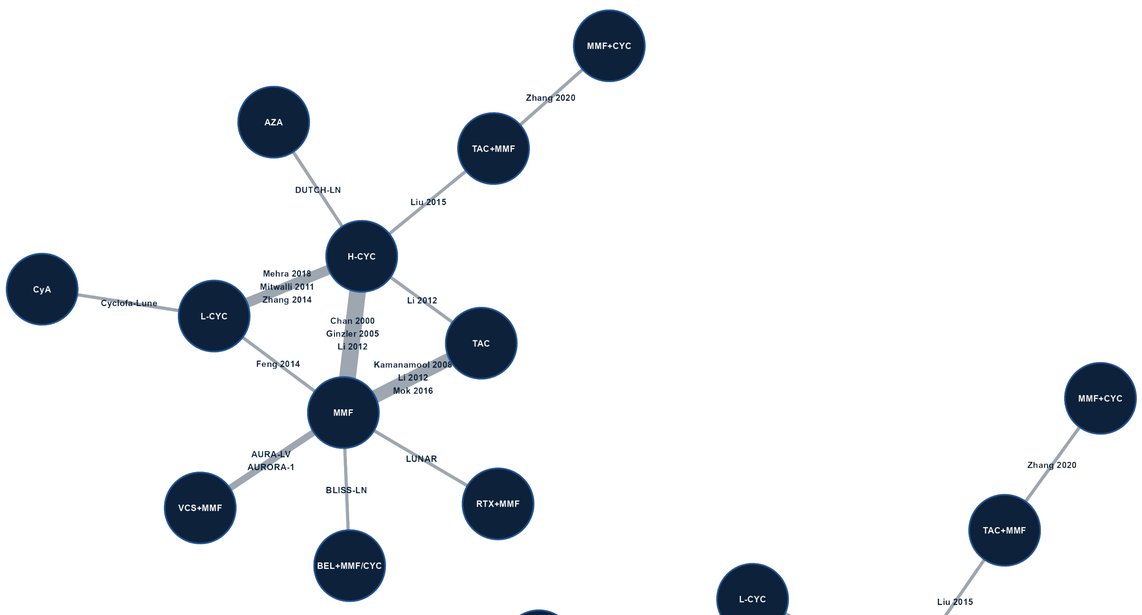
- Electronic database searches were conducted on 24th January, 2022 for randomized controlled trials (RCTs) of therapies used in the treatment of adult patients with active LN class III, IV or V (including mixed class III/V and IV/V). Searches were conducted in MEDLINE®, MEDLINE In-Process, Embase® and Cochrane Central Register of Controlled Trials (CENTRAL), accompanied with a conference hand-search. Comparators included treatments utilized in European practice: azathioprine (AZA), belimumab (BEL), cyclophosphamide (CYC), cyclosporin A (CyA), mycophenolate mofetil (MMF), rituximab (RTX) and tacrolimus (TAC). The outcome of interest was complete renal response (CR).
- The feasibility assessment identified certain areas of heterogeneity of the studies included:
  - Heterogenous follow-up
  - Sample size
  - Differences in baseline characteristics identified as potential effect modifiers (UPCR, % patients with low eGFR [estimated glomerular filtration rate], duration of LN diagnosis at start of study, dose of concomitant therapies [e.g., corticosteroids, MMF], and % of patients with biopsy class V and prior treatment lines)
  - Heterogenous outcome definitions for CR
  - Follow-up was explored in scenario analyses; all other factors were not adjusted for
- Evidence was synthesized via Bayesian network meta-analysis (NMA) using random effects models for binomial outcomes with a logit link function. Models were ran using the *multinma* package through the user interface to Stan in R (*Rstan*).
- Informative-prior distributions for the between study-heterogeneity parameter were fitted as per Turner et al (2015); log-normally distributed with a mean of -2.93 and standard deviation of 1.58.
- Treatment ranking was calculated using the surface under the cumulative ranking curve (SUCRA). If a treatment always ranks first, then the SUCRA is 100%, whereas if it always ranks last, the SUCRA is 0%. Odds ratios (ORs) and associated 95% credible intervals (CrIs) were then estimated for all analyses. The base case uses the longest follow-up available from each study, however, due to the heterogeneity in follow-up time, two scenario analyses were conducted by limiting the networks to CR reported at 6 months and CR reported at 12 months or later to assess the effect of follow-up heterogeneity.

RESULTS

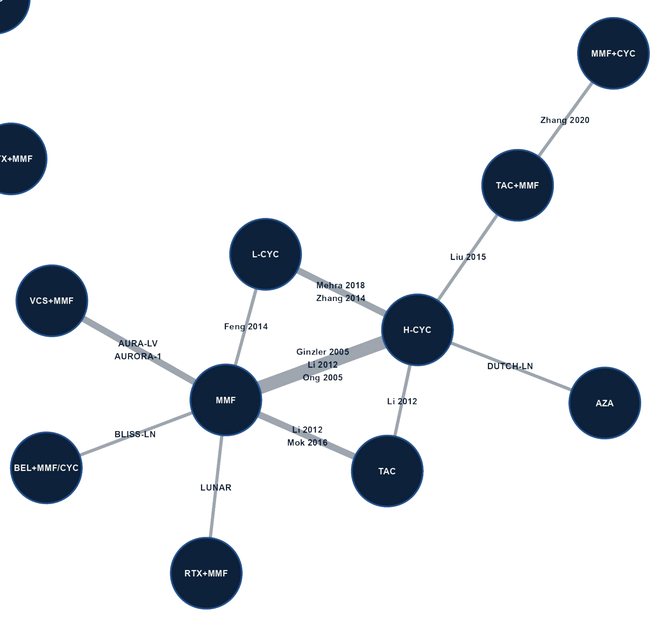
Networks of evidence

- Following the feasibility assessment, 19 RCTs were included in the NMA. The networks formed by the included studies are presented in Figure 1 for the base case (Figure 1a) and scenario analyses at 6 months (Figure 1b) and 12 months or later (Figure 1c). Due to a lack of available evidence, CyA was not possible to include in the 6 months network, while TAC+MMF and MMF+CYC were not possible to include in the 12 months or later network. The results are given against the reference treatment of MMF.

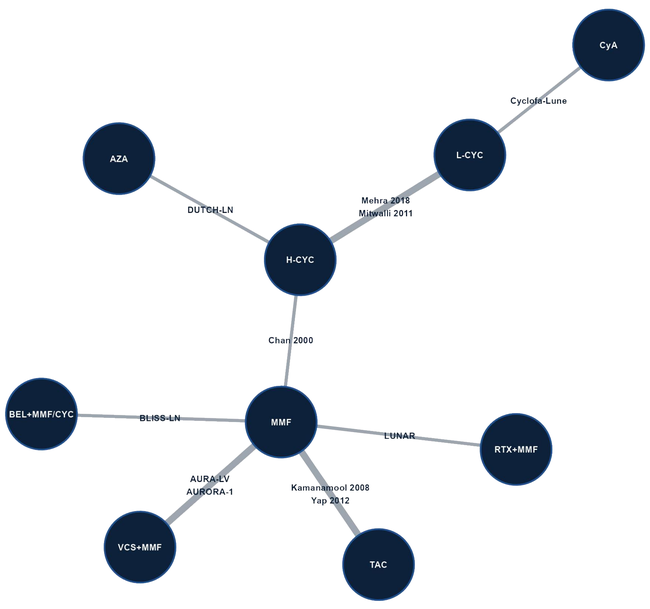
Figure 1. Network plots of trials included in the all-evidence network, 6-month only and 12-month or later analyses



a) Base case analysis



b) Scenario analysis, follow-up 6 months



c) Scenario analysis, follow-up at least 12 months

RESULTS

Network meta-analysis

Results for all analyses are reported in Figure 2.

1. Base case

In the base case, VCS+MMF demonstrated significantly favorable efficacy versus MMF alone (OR: 2.67, 95% CrI: 1.73-4.15). Other CNIs such as TAC (both monotherapy and in combination with MMF) and CyA did not show significantly favorable efficacy versus MMF.

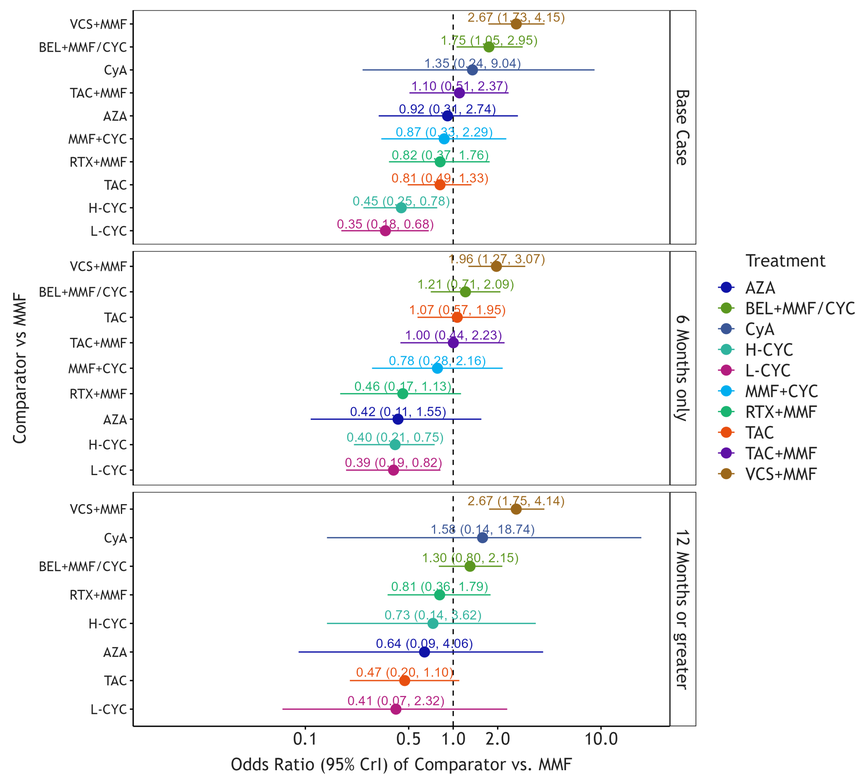
2. Scenario analysis, follow-up of 6 months

In the scenario analysis of 6-months follow-up, VCS+MMF was the only intervention which demonstrated significantly favorable efficacy versus MMF alone (OR: 1.96, 95% CrI: 1.27-3.07), in terms of achieving CR.

3. Scenario analysis, follow-up of at least 12 months

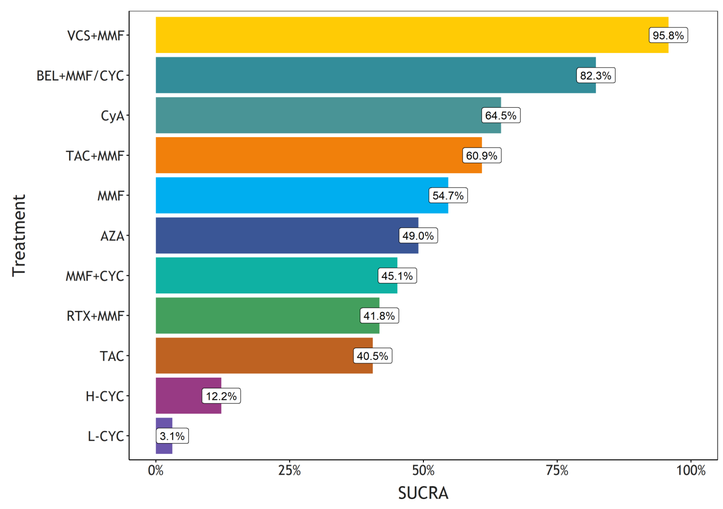
VCS+MMF demonstrated significantly favorable efficacy over MMF alone (OR: 2.67, 95% CrI: 1.75-4.14) and, as in the 6-month scenario, was the only treatment to demonstrate significantly greater efficacy than MMF with regards to achieving CR.

Figure 2. Results of NMA analysis versus MMF



- The SUCRA plot (Figure 3) provides a numerical summary of the cumulative ranking of treatments. The SUCRA shows that VCS+MMF is highly likely to be the preferred treatment option (SUCRA value = 95.8%) followed by BEL+MMF/CYC (SUCRA value = 82.3%) and CyA (SUCRA value = 64.5%).

Figure 3. SUCRA plot, base case



LIMITATIONS

- This NMA highlights the limitations faced when performing comparative analysis in LN, including:
  - Heterogenous follow-up times, with most trials reporting at 6 months, meaning longer-term outcomes are difficult to compare.
  - Heterogenous definitions of CR, some trials have a more stringent definition of CR (e.g., AURORA including UPCR threshold of ≤0.5mg/mg vs ≤0.7mg/mg in BLISS-LN).
  - Imbalances in baseline characteristics and potential treatment effect modifiers.
  - Quality of evidence e.g.,
    - Low sample size in some studies.
    - Trials investigating tacrolimus focused on Asian-only populations, limiting generalisability to European clinical practice.
    - Lack of reporting - e.g., heterogeneity is present in some patient characteristics, such as prior lines of therapy, but few trials reported on this.

CONCLUSIONS

- These analyses find that VCS+MMF is highly likely (SUCRA 96%) to be the preferred treatment option for achieving CR in active LN compared to all other therapies included. ORs for CR favored VCS+MMF, with VCS+MMF being the only treatment with significantly favorable efficacy compared to MMF in all analyses conducted.
- However, it is challenging to conduct NMAs in LN due to the heterogeneity in the evidence base due to the reasons outlined above. As such, results of NMAs conducted in LN should be interpreted with caution.

REFERENCES

1. Rovin et al., Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2021, 397(10289):2070–2080.
2. Dias et al., A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. Published online 2011.
3. Phillipo, *Multinma: Network Meta-Analysis of Individual and Aggregate Data in Stan.*; 2021.
4. Fanouriakis et al., 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis*. 2020, 79(6):713-23.
5. Rohatgi, *WebPlotDigitizer*. Austin, Texas, USA; 2017.
6. Salanti et al., Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol*. 2011, 64(2):163-171.
7. Turner et al., Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Statistics in medicine*. 2015, 34(6): 984-998

DISCLOSURES

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