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Feasibility Assessment of Indirect Treatment Comparisons in Relapsed Polymyalgia Rheumatica: Evidence Availability and Methodological Considerations

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KEY FINDINGS & CONCLUSIONS

- A systematic literature review identified 26 publications, of which five studies (REPLENISH, SAPHYR, PMR-MODE, PMR-SPARE, and SEMAPHORE) met the eligibility criteria for detailed comparability assessment.
- Studies evaluating methotrexate or tocilizumab were considered less suitable because of greater heterogeneity and lower comparability with REPLENISH.
- Among the studies assessed for comparability to REPLENISH, SAPHYR was considered the most suitable due to its clinical and methodological similarity.
- An anchored indirect comparison of secukinumab versus sarilumab is technically feasible using the placebo plus GC-taper arms of REPLENISH and SAPHYR as the common comparator; however, differences in GC tapering and potentially unmeasured effect modifiers may limit the clinical validity and interpretability of the findings, and any results should therefore be interpreted with caution.
- An anchored MAIC could serve as the preferred adjusted analysis, with STC considered as an alternative adjusted analysis and an unadjusted Bucher ITC as a sensitivity analysis. However, residual uncertainty due to methodological and clinical heterogeneity is likely to remain despite adjustment.

INTRODUCTION

- Polymyalgia rheumatica (PMR) is an idiopathic rheumatic inflammatory disease affecting adults aged ≥50 years and is characterized by pain and stiffness in the shoulder and pelvic girdles, often accompanied by elevated inflammatory markers.[1,2]
- Although glucocorticoids (GCs) remain the standard treatment, high relapse rates and prolonged GC exposure are associated with substantial toxicity, highlighting the need for effective GC-sparing therapies.[3,4]
- The phase 3 REPLENISH trial demonstrated the efficacy of secukinumab in relapsed PMR[5]; however, without head-to-head studies, indirect treatment comparisons are needed to evaluate its relative efficacy and safety versus alternative therapies.
- **OBJECTIVE:** To assess the feasibility of conducting an indirect treatment comparison (ITC) of the efficacy and safety of secukinumab versus relevant comparators in relapsed PMR.

METHODS

- A systematic literature review (SLR) identified studies evaluating efficacy and safety in adults with PMR.
- Studies meeting predefined eligibility criteria were assessed for clinical and methodological comparability (study design, patient populations, inclusion/exclusion criteria, GC tapering regimens, endpoint definitions, and assessment timepoints).
- ITC assumptions of similarity and heterogeneity were evaluated through comparison of study characteristics, baseline patient populations, prognostic factors (PFs), and treatment effect modifiers (EMs).
- Similarity was assessed using absolute standardized mean differences (ASMDs) for baseline characteristics.
- Heterogeneity and placebo-arm exchangeability were assessed using efficacy and safety outcomes and supported by forest plots, Cochran's Q, and I^2 statistics.
- Transitivity was evaluated by identifying clinically relevant PFs and EMs and assessing their inclusion in adjusted ITC models.
- The feasibility of Bucher ITC, matched adjusted indirect comparison (MAIC), and simulated treatment comparison (STC) approaches was evaluated based on network connectivity, study comparability, and data availability.
- Cross-trial overlap in baseline characteristics was quantitatively assessed using REPLENISH Individual Patient Data (IPD) and published aggregate data to determine the feasibility of adjusted ITC methods.

RESULTS

Study Identification

- An SLR identified 26 publications, of which five studies (REPLENISH, SAPHYR, PMR-MODE, PMR-SPARE, and SEMAPHORE) met the eligibility criteria for detailed comparability assessment.
- SAPHYR (sarilumab) demonstrated the closest clinical and methodological alignment with REPLENISH, despite differences in glucocorticoid (GC) tapering schedules (Table 1).[6]
- PMR-MODE (methotrexate), PMR-SPARE and SEMAPHORE (tocilizumab) showed limited comparability due to differences in patient populations, GC taper regimens, endpoint definitions, and outcome reporting (Table 1).[7-9]
- Overall, SAPHYR was considered the most suitable study for comparative analyses, whereas the remaining studies were considered infeasible for meaningful comparison because of substantial clinical and methodological differences.

Table 1. Comparison of identified studies

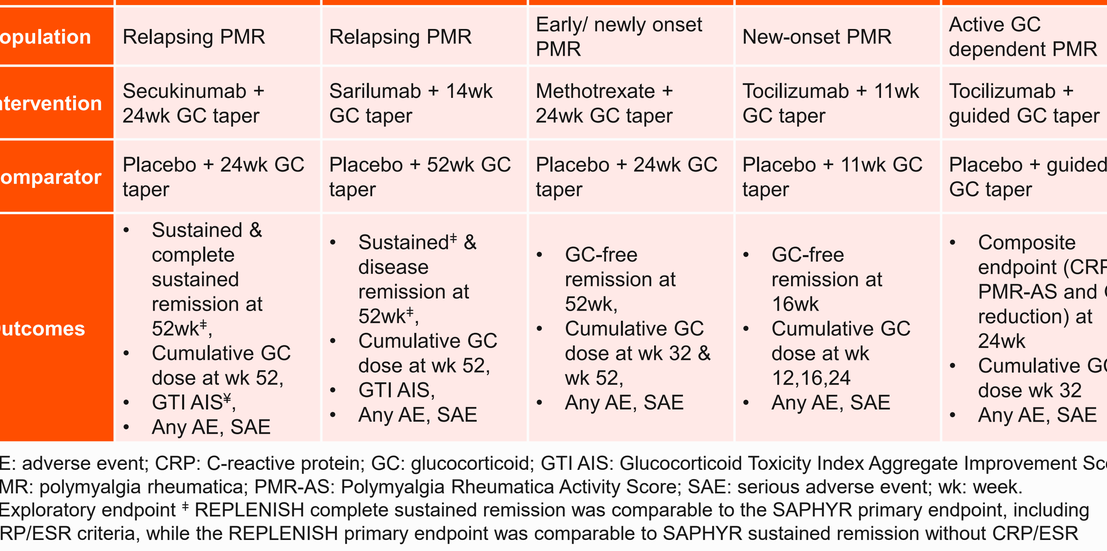
	REPLENISH[5]	SAPHYR[6]	PMR-MODE[7]	PMR-SPARE[8]	SEMAPHORE[9]
Population	Relapsing PMR	Relapsing PMR	Early/ newly onset PMR	New-onset PMR	Active GC dependent PMR
Intervention	Secukinumab + 24wk GC taper	Sarilumab + 14wk GC taper	Methotrexate + 24wk GC taper	Tocilizumab + 11wk GC taper	Tocilizumab + guided GC taper
Comparator	Placebo + 24wk GC taper	Placebo + 52wk GC taper	Placebo + 24wk GC taper	Placebo + 11wk GC taper	Placebo + guided GC taper
Outcomes	• Sustained & complete sustained remission at 52wk‡, • Cumulative GC dose at wk 52, • GTI AIS¥, • Any AE, SAE	• Sustained‡ & disease remission at 52wk‡, • Cumulative GC dose at wk 52, • GTI AIS, • Any AE, SAE	• GC-free remission at 52wk, • Cumulative GC dose at wk 32 & wk 52, • Any AE, SAE	• GC-free remission at 16wk • Cumulative GC dose at wk 12,16,24 • Any AE, SAE	• Composite endpoint (CRP PMR-AS and GC reduction) at 24wk • Cumulative GC dose wk 32 • Any AE, SAE

AE: adverse event; CRP: C-reactive protein; GC: glucocorticoid; GTI AIS: Glucocorticoid Toxicity Index Aggregate Improvement Score; PMR: polymyalgia rheumatica; PMR-AS: Polymyalgia Rheumatica Activity Score; SAE: serious adverse event; wk: week.
¥ Exploratory endpoint ‡ REPLENISH complete sustained remission was comparable to the SAPHYR primary endpoint, including CRP/ESR criteria, while the REPLENISH primary endpoint was comparable to SAPHYR sustained remission without CRP/ESR

Baseline Similarity Assessment

- Baseline similarity between REPLENISH and SAPHYR was assessed using study-level comparisons and ASMD analyses of key patient characteristics.
- Covariate balance was evaluated in both the overall trial populations and placebo arms (Figure 1).
- Using an ASMD threshold of >0.1, meaningful between-study imbalances were observed for race distribution, prior methotrexate use, CRP, ESR, and baseline prednisolone dose, with CRP showing the largest imbalance (ASMD=0.814). Shoulder pain symptoms were imbalanced only in the placebo-arm comparison.

Figure 1. Assessment of covariate balance (REPLENISH vs SAPHYR)



The purple dots represent the ASMD for each baseline covariate, and the red dashed vertical line indicates the prespecified imbalance threshold (ASMD = 0.10). Covariates with ASMD values above 0.10 may be considered meaningfully imbalanced between studies. The left panel presents the assessment of common-arm exchangeability based on the placebo arms only, whereas the right panel presents the assessment of study-level exchangeability using both treatment arms pooled.

Common-Comparator Assessment

- REPLENISH and SAPHYR both included placebo plus GC taper as the common comparator, enabling consideration of an anchored ITC. A key design difference was the GC taper duration: 24 weeks in REPLENISH versus 52 weeks in SAPHYR.
- Placebo-arm outcomes were compared descriptively across the available efficacy and safety endpoints. Given the inclusion of only two trials, Cochran's Q and I^2 could not reliably establish exchangeability of the common comparator.
- The difference in GC taper duration was identified as an important clinical and design limitation that may limit interpretation of the ITCs.

Covariate Assessment

- Clinically relevant PFs and EMs were identified through expert medical input (*medical set*) and published evidence (*Boyadzhieva set*[10] and *Dejaco set*[11]) (Table 2).
- Linear Programming (LP) analyses indicated that the selected SAPHYR aggregate covariate targets were within the feasible matching region of the REPLENISH IPD for all evaluated covariate sets (Table 2).

Table 2. LP solve results based on covariates from REPLENISH and SAPHYR trials

Covariate set	Covariates	MAIC feasible?
Medical set	Age, sex, CRP, prednisolone at baseline, disease duration, morning stiffness >45 min	Yes, based on LP assessment
Boyadzhieva set[10]	Age, sex, ESR, CRP, disease duration	Yes, based on LP assessment
Dejaco set[11]	Age, sex, ESR, CRP, prior treatment: MTX, Prednisolone at baseline	Yes, based on LP assessment

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LP: Linear programming; MTX: Methotrexate
Note: An LP solve result of 0 indicates that exact matching is feasible for the selected covariate set and supports the feasibility of MAIC.

Potential Indirect Comparison Approaches

- An anchored indirect comparison of secukinumab versus sarilumab via the placebo plus GC taper arms of REPLENISH and SAPHYR could be conducted.
- Anchored MAIC could be considered as the adjusted analysis, as REPLENISH IPD are available and observed imbalances in potential effect modifiers can be addressed through reweighting.
- STC, which also uses IPD but requires an outcome regression model, could be considered as an alternative adjusted analysis.
- An unadjusted Bucher ITC could be conducted, as a sensitivity analysis to assess the impact of population adjustment.

Limitations

- The anchored comparison assumes consistency of relative treatment effects across trials. With only two trials, heterogeneity and exchangeability of the common comparator cannot be reliably assessed.
- The difference in GC taper duration between REPLENISH and SAPHYR represents an important clinical and design limitation that may influence comparative estimates.
- Differences in baseline characteristics and the availability or reporting of potential EMs may limit cross-trial adjustment.
- MAIC can only adjust for observed and reported characteristics and cannot address unmeasured confounding or residual differences in study design.
- LP feasibility establishes numerical support for matching selected covariate means but does not guarantee an adequate effective sample size or stable weights.

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