Effectiveness of IL-6 Receptor Inhibitors versus Methotrexate or any Conventional Immunomodulators in Patients with Steroid Refractory Polymyalgia Rheumatica

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INTRODUCTION

- PMR is common in people aged ≥50 years[1]
- Primary treatment: GCs[1]

- Treatment for GC refractory patients
  - csIM
  - IL-6Ri
- Commonly used csIM: MTX[2]

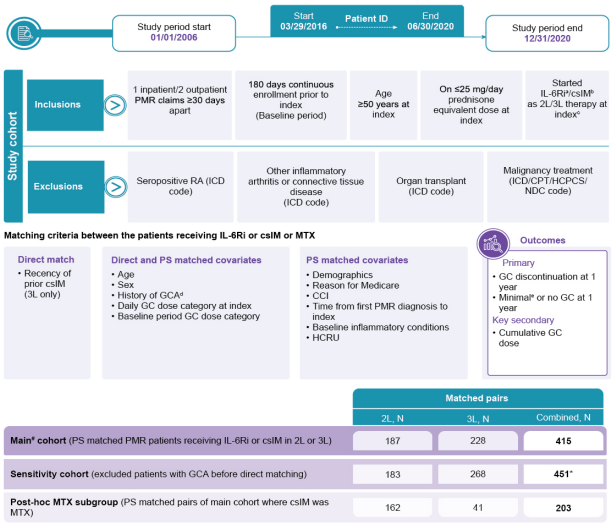
- No direct evidence for IL-6Ri vs. csIM or vs. MTX in PMR patients[3]
- Residual matching concerns in a recent real-world study[2]

OBJECTIVE

- To compare the effectiveness of IL-6Ri vs. csIM or vs. MTX for treatment of GC refractory patients with PMR.

METHODS

Figure 1: Study population and outcomes



	Matched pairs		
	2L, N	3L, N	Combined, N
Main[a] cohort (PS matched PMR patients receiving IL-6Ri or csIM in 2L or 3L)	187	228	**415**
Sensitivity cohort (excluded patients with GCA before direct matching)	183	268	**451**[f]
Post-hoc MTX subgroup (PS matched pairs of main cohort where csIM was MTX)	162	41	**203**

[a]Sarilumab, tocilizumab; [b]methotrexate, leflunomide, azathioprine; [c]for 2L, index was the start date of IL-6Ri or csIM with no prior use of IL-6Ri or csIM; index date in 3L was the start date of IL-6Ri or new csIM after prior csIM; [d]not applicable for sensitivity cohort; [e]prednisone equivalent dose ≤2 mg/day.
[f]Direct match criteria amended to address potential residual confounders; [g]by excluding patients with GCA before direct matching, the number of direct match criteria decreased, resulting in higher number of direct matches for the sensitivity cohort vs. the main cohort.

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CONCLUSIONS

- To our knowledge this is the first direct comparison that supports the recent French Society of Rheumatology recommendations to consider IL-6Ri before MTX.
- IL-6Ri was a more effective steroid sparing therapy than csIM or MTX and has the potential to reduce exposure to GC in PMR.

RESULTS

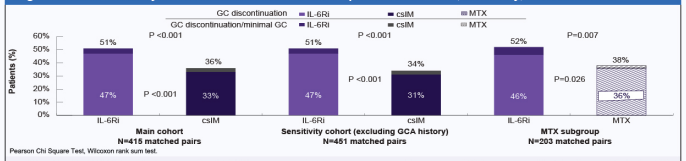
Table 1: Characteristics of PMR patients receiving IL-6Ri or csIM as 2L or 3L therapy after PS match in the main and sensitivity cohort and MTX subgroup

	Main cohort (N=415 matched pairs*)		Sensitivity cohort (N=451 matched pairs*)		MTX subgroup (N=203 matched pairs*)	
Characteristics[a]	csIM	IL-6Ri	csIM	IL-6Ri	MTX	IL-6Ri
Age, years, mean (SD)	75.2 (5.8)	74.8 (6.4)	74.2 (5.6)	74.4 (6.2)	75.5 (5.8)	75.6 (6.9)
Gender, female, n (%)	310 (74.7%)	298 (71.8%)	339 (75.2%)	327 (72.5%)	149 (73.4%)	144 (70.9%)
Race, white, n (%)	377 (90.8%)	373 (89.9%)	405 (89.8%)	405 (89.8%)	178 (87.7%)	177 (87.2%)
CCI, mean (SD)	2.5 (1.8)	2.4 (2.0)	2.4 (1.9)	2.4 (1.9)	2.4 (1.6)	2.5 (2.0)
Time from PMR diagnosis code to index, days, median (IQR)	499 (198, 1,177)	491 (187, 1,148)	451 (170, 1,260)	513 (199, 1,257)	420 (159, 817)	374 (151, 843)
Baseline GC dose, mg/day, mean (SD)	8.4 (6.6)	8.7 (6.3)	7.8 (4.7)	8.0 (5.2)	9.7 (7.9)	10.1 (7.6)
GC dose at index, mg, mean (SD)	11.1 (6.3)	11.0 (6.0)	10.7 (6.0)	10.6 (5.7)	11.8 (6.3)	11.4 (6.1)
History of GCA without PMR, all available data,n (%)	33 (8.0%)	33 (8.0%)	NA	NA	23 (11.3%)	23 (11.3%)
Seronegative RA[§] during baseline period, n (%)	214 (51.6%)	219 (52.8%)	257 (57.0%)	257 (57.0%)	73 (36.0%)	77 (37.9%)

*IL-6Ri and csIM patients were PS matched for both 2L and 3L on region, calendar year, baseline GC dose, COPD, seronegative RA, and outpatient office visits; for 2L only on Crohn's disease, psoriasis, UC, and baseline inpatient days; and for 3L only on age, index day GC dose category, and asthma.
[a]Region, original reason eligible for Medicare, duration of baseline GC therapy, baseline comorbidities (asthma, AD, COPD, Crohn's disease, psoriasis, UC), baseline HCRU (inpatient, outpatient, emergency room visits) were also analyzed and not significantly different between the exposure arms.
[§]Seronegative RA was allowed, given patients can meet classification criteria for both PMR and seronegative RA and may represent initial misdiagnosis or use of ICD-10 codes to obtain reimbursement for off-label use in PMR.

- Patient characteristics were similar between exposure arms after PS match (**Table 1**).

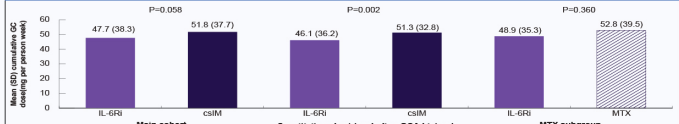
Figure 2: Outcomes at 1 year in PS matched IL-6Ri and csIM patients in the main, sensitivity, and MTX cohort



Pearson Chi Square Test, Wilcoxon rank sum test.

- About half of PMR patients receiving IL-6Ri were able to discontinue or get to minimal GC use vs. only about one-third of csIM initiators (**Figure 2**).

Figure 3: Mean (SD) cumulative GC dose (mg per person week) at 1 year in PS matched patients in the main, sensitivity, and MTX cohort



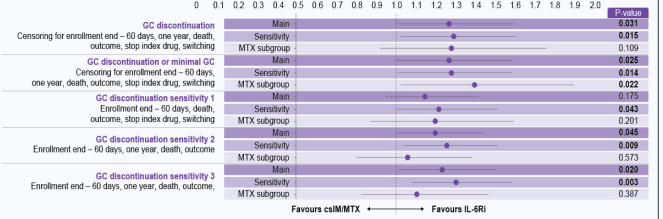
GC dose expressed as prednisone equivalents. Pearson Chi Square Test, Wilcoxon rank sum test.

- Mean cumulative GC dose was lower for IL-6Ri vs. comparators in all cohorts, and statistically significant in the sensitivity cohort (**Figure 3**).
- Results for cohorts that included patients matched on history of GCA (main and MTX cohorts) may have been impacted by the high variability (SD) in GC dose and/or presence of residual confounders indicated by higher GC dose in the IL-6Ri arm during the first 90 days for these cohorts (**Table 2**).

In the csIM arm of **main and sensitivity cohort**, the most used index csIM was:
- 2L: MTX (main, 162/187 [86.6%]; sensitivity, 160/183 [87.4%]).
- 3L: LEF (main, 162/228 [71.1%]; sensitivity, 193/268 [72.0%]).

In the **MTX subgroup** analysis in 3L, the most common prior csIM was:
- IL-6Ri arm: MTX (32/41 [78.0%]).
- MTX arm: LEF (37/41 [90.2%]).

Figure 4: Hazard ratio[a] for IL-6Ri vs. csIM (main[a] and sensitivity[b] cohort) or vs. MTX[c] in the combined cohort after PS match stratified by 2L and 3L



*For time to event analysis, Cox models were used to estimate hazard ratios with 95% CI.
[a]Adjusted for age, region, original reason for Medicare, baseline weekly prednisone equivalent dose, COPD, seronegative RA, and GCA. [b]adjusted for gender, index day prednisone equivalent dose, asthma, COPD, emergency department visits number, original reason eligible for Medicare, CCI category, AD. [c]no adjustments were made as the differences were not statistically different.

- For the combined 2L/3L cohort, IL-6Ri vs. csIM patients were significantly more likely to discontinue GC at 1 year in the main and sensitivity cohorts and favored IL-6Ri vs. MTX (**Figure 4**).
  - IL-6Ri vs. MTX patients were significantly more likely to discontinue GC at 1 year in 2L (HR [95% CI]: 1.41 [1.00, 1.98], P=0.048).
- IL-6Ri vs. csIM or vs. MTX patients were significantly more likely to be on minimal/no GC in all cohorts at 1 year (**Figure 4**).

Table 2: Change in weekly prednisone equivalent dose from baseline by period in the IL-6Ri group, referent to csIM or MTX for combined cohort after PS match

	Main cohort (IL-6Ri vs. csIM; matched on GCA history)		Sensitivity cohort (IL-6Ri vs. csIM; no GCA history)		MTX subgroup (IL-6Ri vs. MTX)	
Matched pairs, N	415		451		203	
Change in weekly prednisone equivalent dose	Beta (95% CI)	P-value	Beta (95% CI)	P-value	Beta (95% CI)	P-value
Day 1-365 from baseline/censoring for enroll end-60, index date + 365, death, outcome, stop index drug, switching						
IL-6Ri	−6.03 (−12.6, 0.537)	0.072	−6.77 (−11.9, −1.60)	**0.010**	−7.30 (−18.0, 3.42)	0.182
Day 1-365 from baseline/censoring for enroll end, index date + 365, death						
IL-6Ri	−2.13 (−8.30, 4.03)	0.498	−2.26 (−7.04, 2.51)	0.352	−4.19 (−15.0, 6.65)	0.448
Day 1-90 from baseline/censoring for enroll end, index date + 90, death						
IL-6Ri	1.35 (−10.7, 13.4)	0.826	−0.126 (−10.3, 10.0)	0.981	0.191 (−10.7, 11.1)	0.973
Day 91-180 from baseline/censoring for enroll end, index date + 180, death						
IL-6Ri	−3.55 (−10.4, 3.29)	0.309	−2.20 (−7.61, 3.20)	0.424	−4.42 (−15.9, 7.08)	0.450
Day 181-270 from baseline/censoring for enroll end, index date + 270, death						
IL-6Ri	−2.70 (−9.68, 4.26)	0.447	−2.33 (−7.91, 3.24)	0.411	−6.09 (−17.8, 5.64)	0.308
Day 271-365 from baseline/censoring for enroll end, index date + 365, death						
IL-6Ri	−7.11 (−14.3, 0.065)	0.052	−9.44 (−15.2, −3.66)	**0.001**	−10.4 (−22.2, 1.41)	0.084

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ABBREVIATIONS
2L, second line; 3L, third line; AD, atopic dermatitis; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPT, current procedural terminology; csIM, conventional synthetic immunomodulators; GC, glucocorticoids; GCA, giant cell arteritis; HCPCS, healthcare common procedure coding system; HCRU, healthcare resource utilization; HR, hazard ratio; ICD10, international classification of diseases, tenth revision; IL-6Ri, IL-6 receptor inhibitors; IQR, interquartile range; LEF, leflunomide; mg, milligrams; MTX, methotrexate; NA, not applicable; NDC, national drug code; PMR, polymyalgia rheumatica; PS, propensity score; RA, rheumatoid arthritis; SD, standard deviation; UC, ulcerative colitis

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