Effectiveness of Interleukin-6 Receptor Inhibitors versus Conventional Synthetic Immunomodulatory Therapy for Treatment of Frail Patients with Polymyalgia Rheumatica

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BACKGROUND

- Frailty is associated with aging and inflammation, leading to increased risk of mortality and morbidity[1]
- Frailty appears to be more prevalent in patients with PMR vs. the general population[1]
- Reducing GC use is important in patients with PMR, particularly with frailty, which may be exacerbated by GC use[2]
- Patients with both PMR and frailty may benefit from IL-6Ri therapy as IL-6 is involved in the pathogenesis of both[1,3]
- A retrospective study showed that a higher proportion of patients on IL-6Ri vs. conventional synthetic immunomodulators (csIM) discontinued GC at 1 year (HR [95% CI]: 1.28 [1.02–1.60][4]

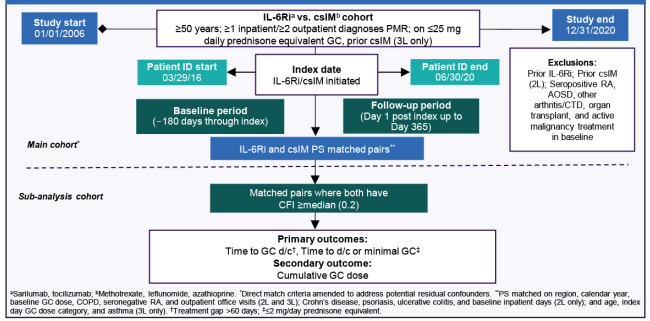
OBJECTIVES

- The study compared the effectiveness of IL-6Ri vs. csIM therapy as second (2L) and third (3L) line treatment in the subgroup of frail patients with PMR

METHODS

- A subgroup analysis of patients with frailty from a retrospective cohort study using Medicare claims data **(Figure 1)**
- IL-6Ri and csIM patients with PMR were direct matched and then propensity score (PS) matched on multiple factors
- PS matched pairs were assessed with a validated claims-based frailty index (CFI), an algorithm for estimation of frailty levels which was based on the evaluation of gait speed, grip strength, and the 2-year risk of death, institutionalization, disability, hospitalization, and prolonged (>30 days) skilled nursing facility stay, in a retrospective cohort study[5]
- Although CFI ≥0.2[6] and ≥0.25[5] have been used as thresholds for frailty, due to sample size CFI ≥median (0.2) was used to identify more frail patients. Matched pairs with CFI ≥0.2 were retained for comparison
- The primary outcomes were time to GC discontinuation (d/c) and time to GC d/c or minimal GC. Cumulative GC dose was also compared

Figure 1: Study design



[a]Sarilumab, tocilizumab; [b]Methotrexate, leflunomide, azathioprine. *Direct match criteria amended to address potential residual confounders. **PS matched on region, calendar year, baseline GC dose, COPD, seronegative RA, and outpatient office visits (2L and 3L); Crohn's disease, psoriasis, ulcerative colitis, and baseline inpatient days (2L only); and age, index day GC dose category, and asthma (3L only). †Treatment gap >60 days; ‡≤2 mg/day prednisone equivalent.

Presented at the RheumNow Live 2025 Annual Meeting, Dallas, Texas, USA (Feb 8–9, 2025)

CONCLUSION

- **Compared with csIM, IL-6Ri had a greater GC-sparing effect in the main cohort as well as the frailty subgroup of patients with PMR**
- **The treatment effect size seen in patients with frailty appears to be larger than that reported in the main cohort[4]**
- **Frail patients with PMR may derive even greater benefit from IL-6Ri therapy compared with csIM therapy**

RESULTS

- Of the 187 2L and 228 3L PS matched pairs from the main cohort, 89 (35 [39.3%] 2L and 54 [60.7%] 3L) had CFI ≥0.2, the median (frailty subgroup)
- Most common csIM therapy in 2L and 3L, respectively: Main cohort: MTX (86.6%) and LEF (71.1%); Frailty subgroup: MTX (77.1%) and LEF (64.8%)
- Patient characteristics were generally balanced in both the main cohort and the frailty subgroup **(Table 1)**

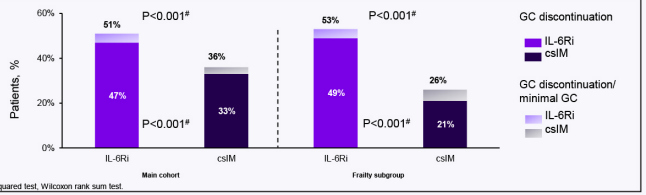
Table 1: Characteristics of patients receiving IL-6Ri or csIM as 2L or 3L therapy after PS match

	Main cohort		Frailty subgroup	
Characteristics*	**IL-6Ri† (N=415)**	**csIM† (N=415)**	**IL-6Ri† (N=89)**	**csIM† (N=89)**
Age at index, years[a,b]**	74.8 (6.4)	75.2 (5.8)	77.2 (6.6)	76.0 (6.5)
Gender, female[a,b]**	298 (71.8%)	310 (74.7%)	70 (78.7%)	69 (77.5%)
Race, white[b]**	373 (89.9%)	377 (90.8%)	81 (91.0%)	77 (86.5%)
Reason for Medicare enrollment, age ≥65 years[b]**	360 (86.7%)	361 (87.0%)	72 (80.9%)	61 (68.5%)
Daily GC dose# during baseline (mg)[c]**	8.7 (6.3)	8.4 (6.6)	8.1 (5.0)	8.4 (5.4)
Daily GC dose# category during baseline[a,b]**				
<2.5 mg	37 (8.9%)	42 (10.1%)	<11	<11
2.5–<5 mg	78 (18.8%)	79 (19.0%)	19 (21.3%)	19 (21.6%)
5–<10 mg	174 (41.9%)	183 (44.1%)	39 (43.8%)	40 (45.5%)
10–<15 mg	81 (19.5%)	70 (16.9%)	11 (12.4%)	17 (19.3%)
15–<20 mg	29 (7.0%)	24 (5.8%)	<11	<11
20–25 mg	<11	<11	<11	<11
>25 mg	<11	Redacted	–	–
Daily GC dose# on index date (mg)[c]**	11.0 (6.0)	11.1 (6.3)	11.1 (6.4)	11.7 (6.3)
Daily GC dose# category on index date[a]**				
<2.5 mg	12 (2.9%)	<11	<11	<11
2.5–<5 mg	37 (8.9%)	Redacted	<11	<11
5–<10 mg	125 (30.1%)	140 (33.7%)	30 (33.7%)	32 (36.0%)
10–<15 mg	103 (24.8%)	97 (23.4%)	17 (19.1%)	20 (22.5%)
15–<20 mg	74 (17.8%)	71 (17.1%)	14 (15.7%)	15 (16.9%)
20–25 mg	64 (15.4%)	67 (16.1%)	18 (20.2%)	17 (19.1%)
Time since last csIM use to index (3L only), days[a]**				
1–60	92 (40.4%)	90 (39.5%)	16 (29.6%)	Redacted
61–80	51 (22.4%)	42 (18.4%)	11 (20.4%)	<11
180+	85 (37.3%)	96 (42.1%)	27 (50.0%)	30 (55.6%)
Charlson Comorbidity Index[b]**	2.4 (2.0)	2.5 (1.8)	3.4 (2.4)	3.3 (2.3)
Time from first PMR diagnosis to index date (days)[b]**	831.1 (900.5)	852.5 (938.9)	1233.5(1184.1)	1249.2(1196.1)
Comorbidities during baseline				
Seronegative RA[1,b]	219 (52.8%)	214 (51.6%)	51 (57.3%)	50 (56.2%)
Number inpatient days during baseline[b]**	0.9 (3.7)	0.7 (2.3)	2.1 (6.2)	0.9 (2.6)
Number emergency department visits during baseline[b]**	0.4 (1.0)	0.5 (1.1)	0.7 (1.1)	0.8 (1.6)
Number outpatient office visits during baseline[b]**	10.1 (5.5)	10.1 (5.4)	11.7 (6.0)	11.5 (5.5)

*Unless otherwise stated continuous variables are reported as Mean (SD) and categorical as n (%). †To protect patient privacy and avoid potential identification of patients only results with ≥11 patients are reported, and data are redacted when there are >11 patients when such results would allow derivation of the number of patients when <11 are reported; ‡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; #Prednisone equivalents; [a]Covariates used as direct match criterion; [b]Covariates in PS model; [c]Covariates not included in direct match or PS model. All matches were done in the original analysis and matched pairs were kept both or neither.

- IL-6Ri vs. csIM initiators were significantly more likely to discontinue GC and achieve discontinuation of GC or minimal GC dose at 1 year in both the main cohort and the frailty subgroup **(Figure 2, Table 2)**

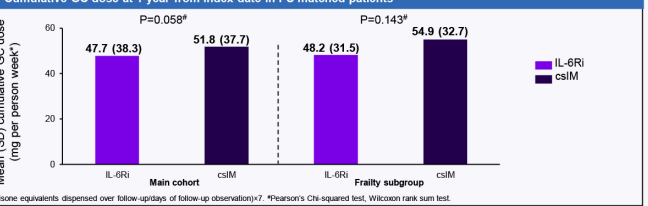
Figure 2: GC discontinuation and GC discontinuation or minimal GC at 1 year from index date in PS matched patients



#Pearson's Chi-squared test, Wilcoxon rank sum test.

- IL-6Ri vs. csIM initiators were found to have a lower cumulative GC dose at 1 year in both the main cohort and the frailty subgroup **(Figure 3)**

Figure 3: Cumulative GC dose at 1 year from index date in PS matched patients



^(Total mg prednisone equivalents dispensed over follow-up/days of follow-up observation)x7. #Pearson's Chi-squared test, Wilcoxon rank sum test.

- Results of sensitivity analyses for discontinuation of GC varying the censoring rules resulted in similar findings in both the main cohort and the frailty subgroup **(Table 2)**

Table 2: Hazard ratios after PS match stratified by 2L and 3L therapy*

		Main cohort		Frailty subgroup	
	Outcome (Censoring rule)	**HR (95% CI)‡**	**P value**	**HR (95% CI)‡**	**P value**
Primary	Discontinue GC (Enrollment end-60 days**, death, outcome, one year, stop index drug, switching)	1.28 (1.02–1.60)	0.031	2.32 (1.35–3.99)	0.002
Primary	Discontinue or minimal GC (Enrollment end-60 days**, death, outcome, one year, stop index drug, switching)	1.28 (1.03–1.58)	0.025	2.23 (1.34–3.71)	0.002
Sensitivity	Discontinue GC (Removing censoring for one year)	1.16 (0.94–1.43)	0.175	1.88 (1.14–3.10)	0.013
Sensitivity	Discontinue GC (Removing censoring for stop index drug, switching)	1.21 (1.00–1.45)	0.045	2.49 (1.59–3.89)	<0.001
Sensitivity	Discontinue GC (Removing censoring for stop index drug)	1.25 (1.04–1.51)	0.020	2.71 (1.71–4.29)	<0.001

*Cox models were used to estimate hazard ratios with 95% CI. **60 days prior to end of enrollment. ‡Adjusted for age, region, original reason for Medicare, baseline weekly prednisone-equivalent dose, COPD, seronegative RA, and GCA. ‡Adjustment of HRs was not required as the difference between groups for all PS match covariates was not statistically significant (P≥0.05).

DISCLOSURES

Sattui SE: Research funding from Bristol Myers Squibb Foundation Robert A. Winn Diversity in Clinical Trials Career Development Award, Research funding from Rheumatology Research Foundation Investigator Award, National Institute of Aging (grant number R03AG082983), Consulting and advisory boards for Sanofi and Amgen (all funds toward research support), Speaker Fees from Fresenius Kabi (all funds toward research support), Research support Amgen and Glaxo Smith Kline (clinical trials), **Dejaco C:** Current abstract Chair for EULAR 2024, Consulting/speaker's fees from AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, Sparrow, Roche, Boehringer, Galapagos, and Sanofi, Editorial board member of the *Annals of the Rheumatic Diseases*; **Ford K, Fiore S and Ackermann M (presenter):** Employees of Sanofi and may hold stock and/or stock options in the company; **Unizony SH:** Research support from Genentech and consulting fees from Kiniksa, Janssen, and Sanofi, **Xie F:** No conflicts of interest; **Curtis JR:** Consulting, research grants from AstraZeneca, Amgen, AbbVie, Bendcare, Genentech, GSK, Horizon, Janssen, Lilly, Novartis, Pfizer, Sanofi, Scipher Medicine, Setpoint, and UCB.

FUNDING

This analysis was funded by Sanofi and Regeneron Pharmaceuticals, Inc.

ACKNOWLEDGEMENTS

- Data included in this poster were originally presented at European Alliance of Associations for Rheumatology (EULAR) 2024, Vienna, Austria (June 12–15, 2024)
- Medical writing support for the original poster (EULAR 2024) was provided by Kritika Dhamija, M.S. (Pharm.), of Sanofi and editorial support for this encore poster was provided by Himani Powle, Pharm D, of Sanofi.

ABBREVIATIONS

AOSD, adult-onset Still's disease; CFI, claims-based frailty index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; csIM, conventional synthetic immunomodulator; CTD, connective tissue disease; d/c, discontinuation; GC, glucocorticoid; GCA, giant cell arteritis; HR, hazard ratio; IL-6Ri, interleukin-6 receptor inhibitor; LEF, leflunomide; MTX, methotrexate; PMR, polymyalgia rheumatica; PS, propensity score; RA, rheumatoid arthritis; SD, standard deviation; 2L, 2nd line; 3L, 3rd line.

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