Generalization of the Effectiveness of Baricitinib 4mg among bDMARD-IR Rheumatoid Arthritis Patients from a RCT to a Real-world Population in China

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Background

- Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation and joint destruction associated with pain, progressive disability, systemic comorbidities and early death[1].
- Baricitinib is an oral selective Janus kinase (JAK) inhibitor (JAK1/JAK2) [2] approved for the treatment of patients with moderate to severe active RA in China.
- Baricitinib 4mg was approved in China for 1) TNFi-IR RA patients or 2) cDMARDs-IR RA patients with inadequate response to baricitinib 2mg for at least 3 months.
- Although randomized controlled trials (RCT) have demonstrated the efficacy of baricitinib 4mg, the generalizability of trial results to Chinese RA patients may be questioned since RCTs lack “external validity”.
- The rationale of the current study is to generate weights and generalize the efficacy results from the RA-BEACON[3] (phase III RCT) of baricitinib 4mg in bDMARDs-IR RA patients to a local Chinese RA population (CREDIT) [4] using reweighting approach.

Objectives

- To generalize the effectiveness of baricitinib 4mg once daily in Chinese bDMARD-IR RA patients from the phase III RCT to a “real-world” population using the reweighting approach.
  - Weights at baseline for RA-BEACON IPD and CREDIT data
  - Generalized effectiveness of baricitinib 4mg versus placebo by ACR20, ACR20 and ACR70 at Week 12
  - Generalized effectiveness of baricitinib 4mg versus placebo by change from baseline to Week 12 in HAQ-DI, DAS28-hsCRP, DAS28-ESR, CDAI and SDAI scores.

Methods

- **Study Design**:This study was a post hoc retrospective analysis using individual patient data (IPD) from the RA-BEACON trial and aggregated data from the CREDIT registry to explore the generalizability of RA-BEACON results to moderate-to-severe RA patients in China

- **Key Inclusion Criteria:**
  - RA-BEACON
    - Age≥18 with moderate to severely active RA
    - Insufficient response or intolerance to previous TNFi treatment
  - CREDIT
    - Registered from 1 January 2016 to 1 July 2021.
    - Age≥18 with active RA
    - Insufficient response to ≥1 bDMARDs

Methods

- **Statistical Analysis**
  - Weights were calculated using IPD from the RA-BEACON trial (phase III RCT, bDMARD-IR patients) and AGR from CREDIT registry in China by generalized method of moments
    - Generalized method of moments is an optimization algorithm subject to the constraints of the first moment equality between selected covariates from both populations
      - Match IPD to AGR with respect to covariates including gender, age, RF/ACPA, ESR, CDAI and CRP
      - Balance achieved after reweighting so as to generalize the effectiveness of baricitinib 4mg versus placebo to the real-world population
  - Weighted Logistic regression was used to evaluate binary effectiveness indicators including ACR20, ACR50 and ACR70
  - Weighted covariance analysis was used to evaluate continuous effectiveness indicators including CDAI, SDAI, DAS28-ESR, DAS28-CRP and HAQ-DI scores
  - Sandwich estimators were utilized for evaluating p-values and 95% CIs of odds ratio and LSM from weighted analyses.

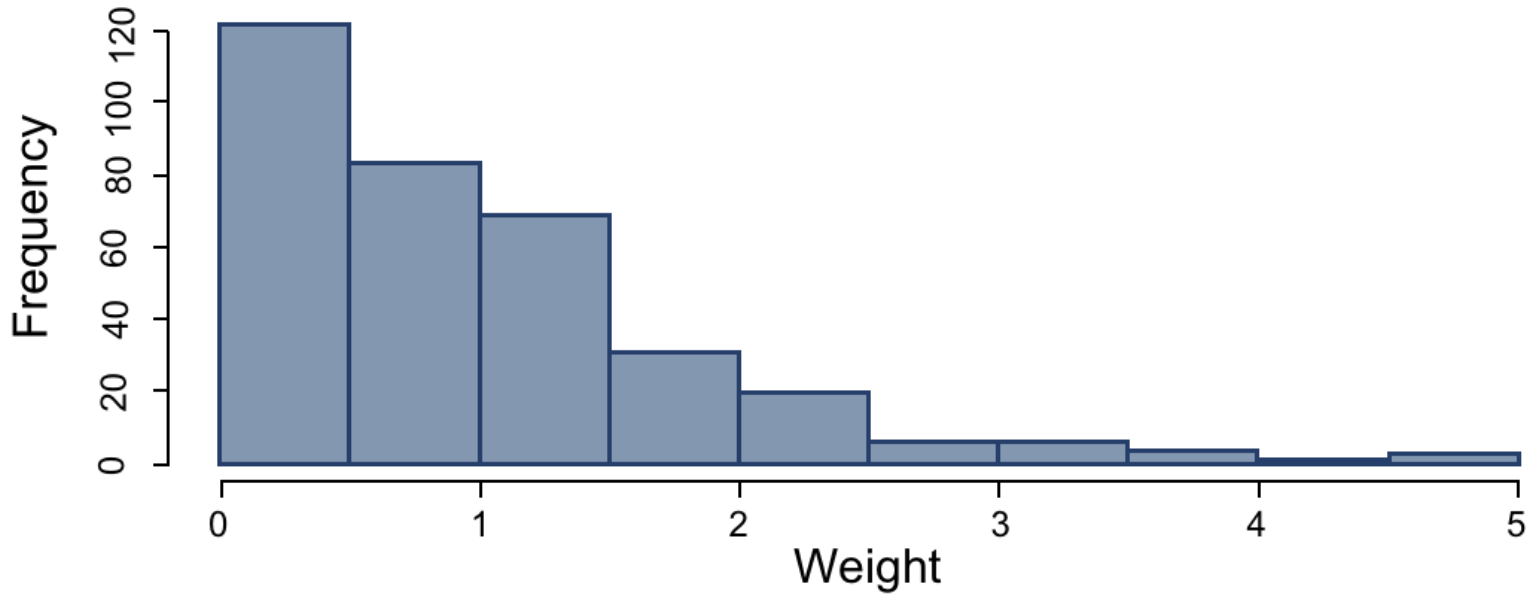
Results: Baseline characteristics matched for reweighting. Non-missing IPD of 343 patients from RA-BEACON were matched to a corresponding CREDIT population of 1006. Balance was achieved after reweighting with respect to covariates including gender, age, RF/ACPA, ESR, CDAI and CRP.

Baseline covariates matched on			
Covariate	**RA-BEACON / Pre-Match/(N=343)**	**RA-BEACON / Post-Match/(N=193.8*)**	**CREDIT (N=1006)**
Gender (Female)	83.1% (285)	80.5% (156)	80.5% (809)
Age	56.2±10.9	52.5±11.8	52.5±12.5
RF/ACPA Positive [Y]§	79.0% (271)	97.3% (189)	97.3% (979)
ESR	47.6±25.0	48.0±25.5	48.0±51.0
CDAI	40.5±13.2	33.6±12.0	33.6±16.0
CRP	20.1±24.8	17.4±19.1	17.4±40.7

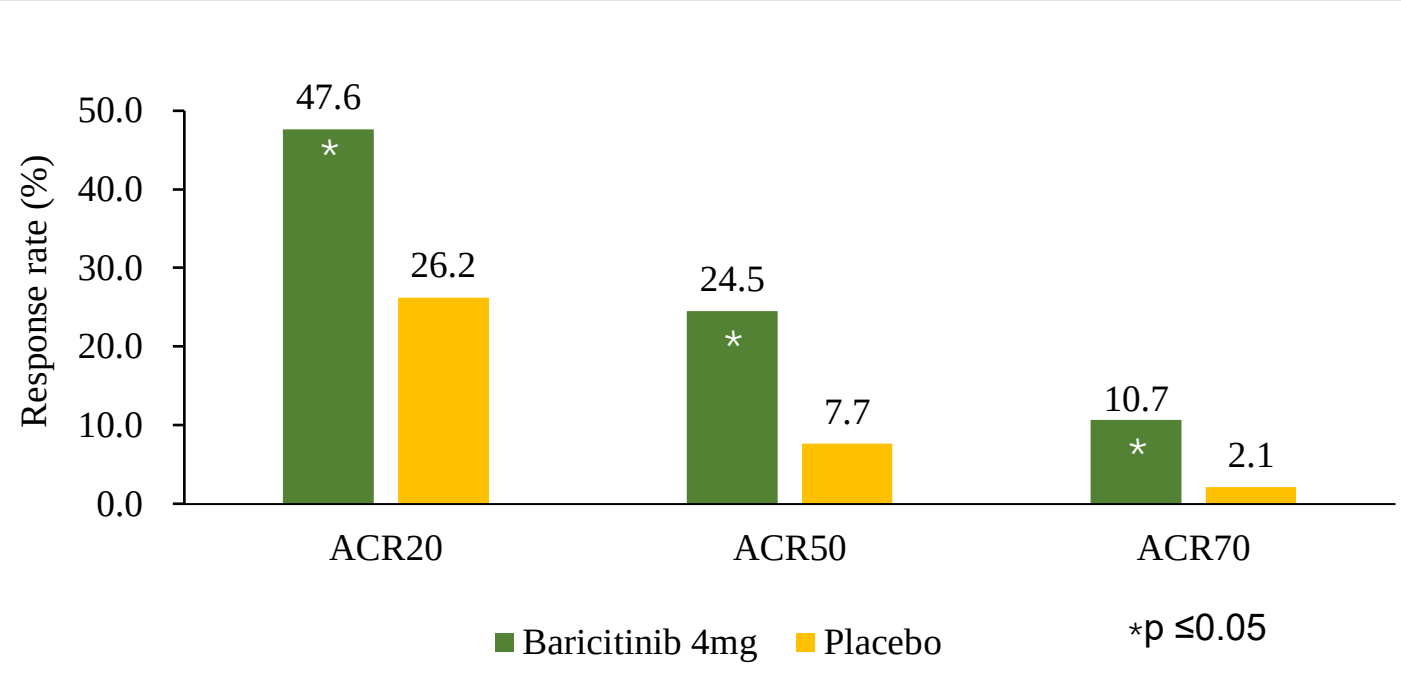
*The Post-Match population (N=193.8) is the effective sample size (ESS), indicating number of patients actually contributing to the analysis based on the size of weights.

§The covariate "RF/ACPA Positive" turns to Y(yes) if the patient has positive RF/positive ACPA/both positive.

Results: Weight distribution. Obtained by generalized method of moments that matches IPD to AGR, weights are smoothly distributed without extreme values.

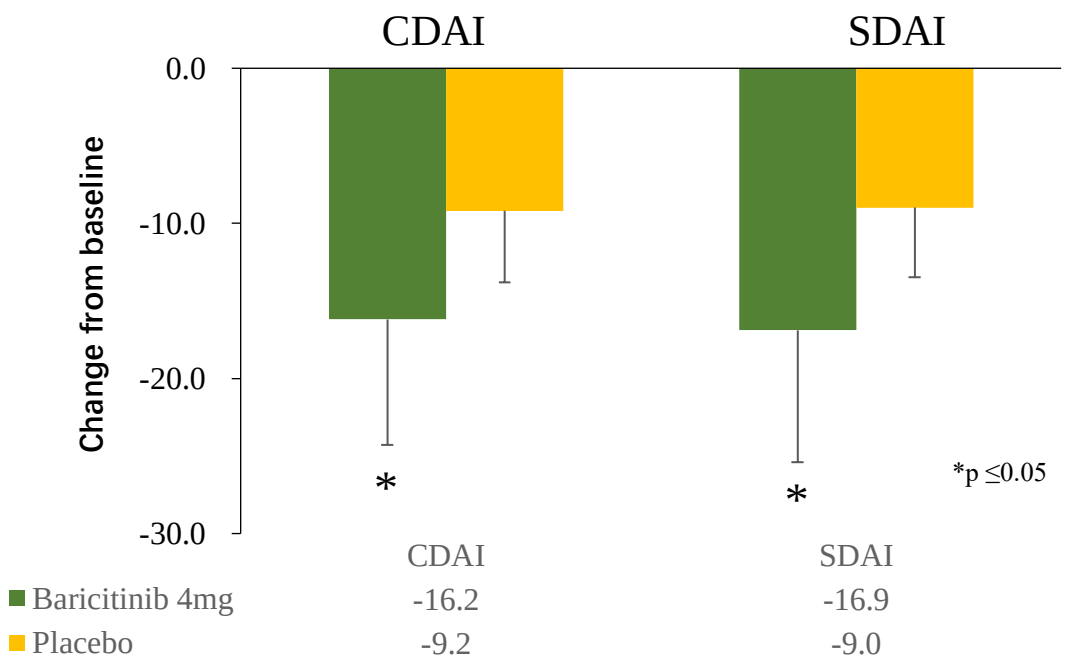


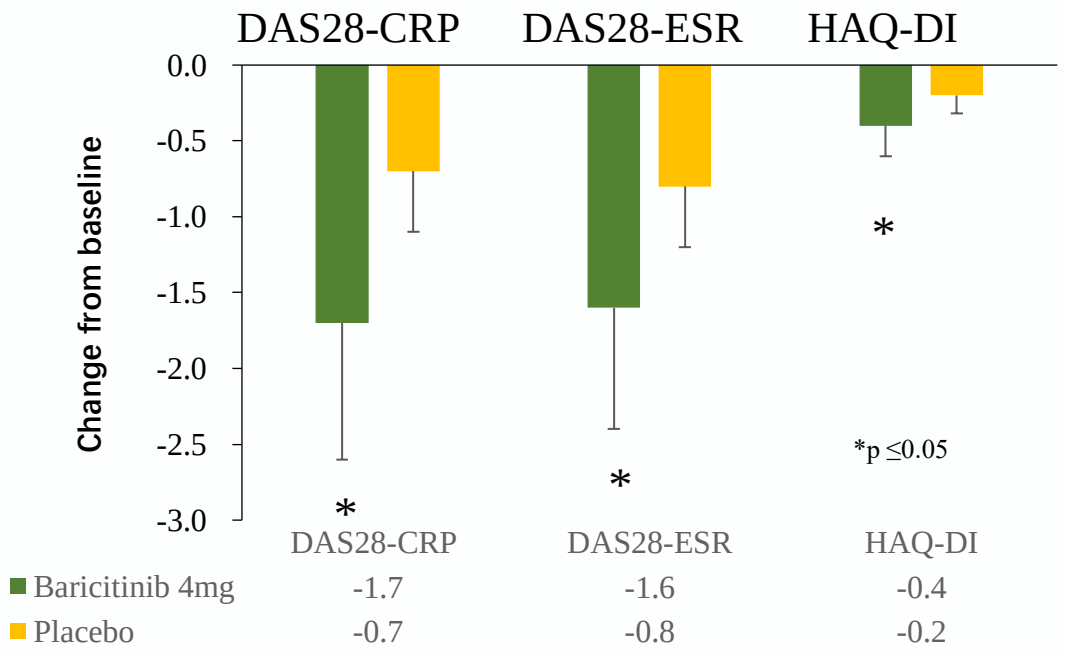
Results: Higher response rates were observed in weighted ACR20 (47.6% vs 26.2%), ACR50 (24.5% vs 7.7%) and ACR70 (10.7% vs 2.1%) scores in patients from the baricitinib 4mg arm compared to the placebo arm at Week 12 ($p \leq 0.05$ for all outcomes). Difference in response rate and odds ratios between arms was evaluated.



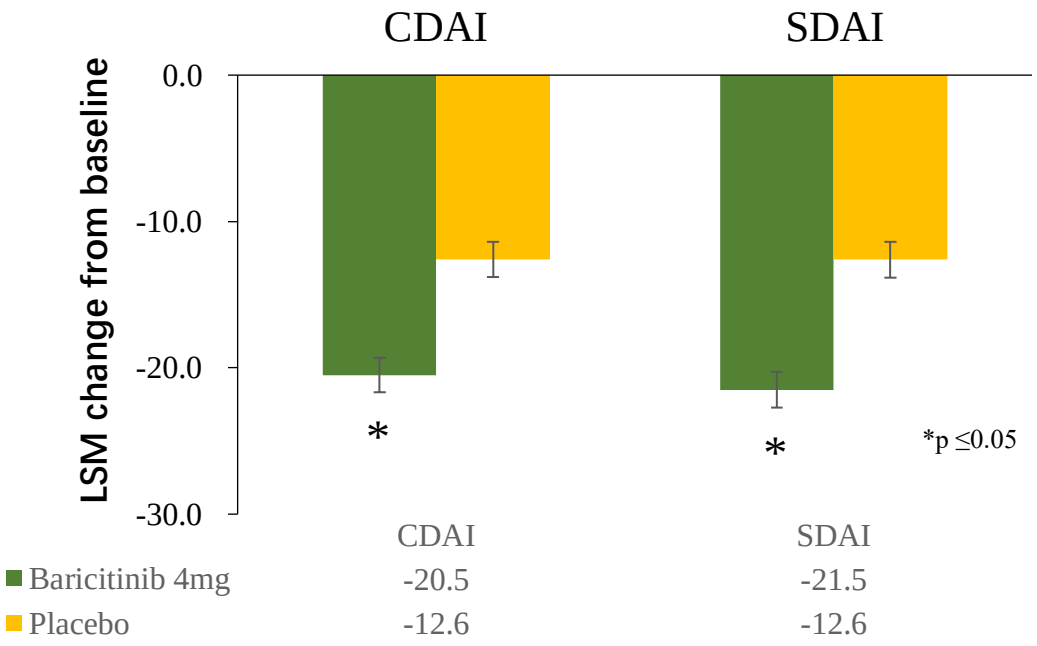
Bari 4 mg vs PBO	ACR20	ACR50	ACR70
Difference in response rate (95% CI)	21.4(11.4,31.3)	16.9(9.3,24.4)	8.5(3.4,13.6)
Odds ratios	2.7(1.5,4.9)	4.3(2.0,9.4)	5.6(1.5,21.7)
P-values	<0.01	<0.01	0.01

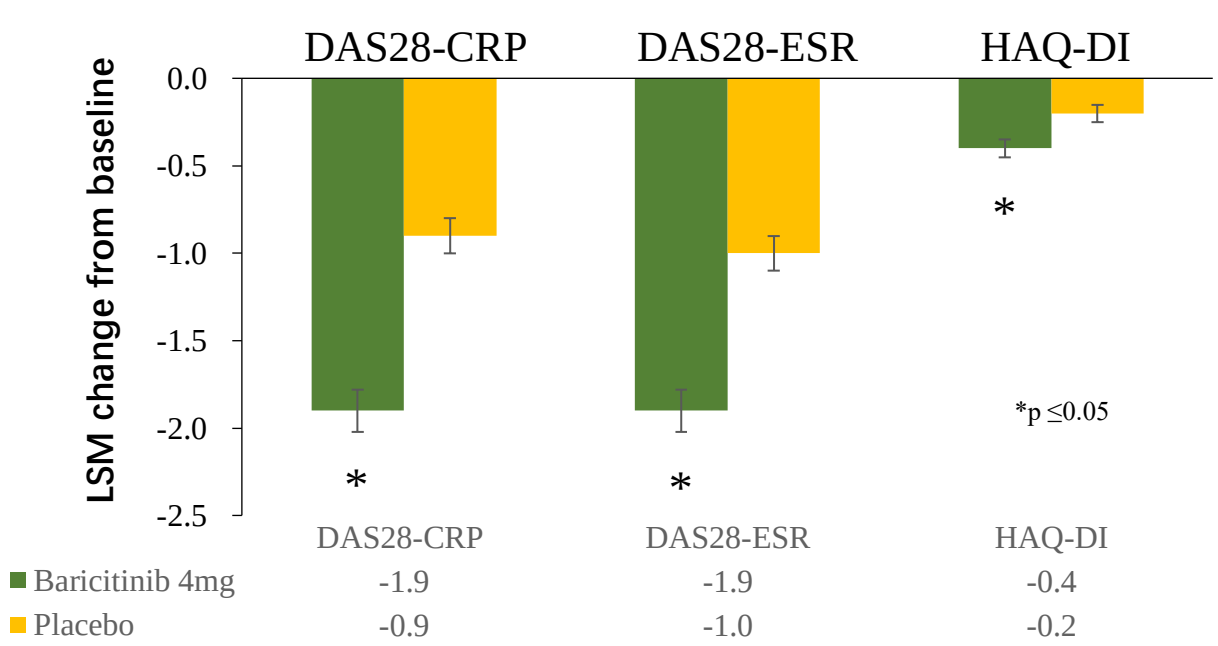
Results: Statistically significant improvements in reweighted CDAI (-16.2 vs -9.2), SDAI (-16.9 vs -9.0), DAS28-CRP (-1.7 vs -0.7), DAS28-ESR (-1.6 vs -0.8) and HAQ-DI (-0.4 vs -0.2) were observed in patients from the baricitinib 4mg arm compared to the placebo arm ($p \leq 0.05$ for all outcomes) at Week 12.





Results: From analysis of covariance with weights (ANCOVA), statistically significant improvements in continuous endpoints(CDAI, SDAI, DAS28-CRP, DAS28-ESR and HAQ-DI) were also observed in patients from the baricitinib 4mg arm compared to the placebo arm ($p \leq 0.05$ for all outcomes) at Week 12.





Conclusions

- Comparable outcomes were observed between the original and reweighted population, indicating the generalizability of efficacy results from the RA-BEACON trial population to the real-world Chinese RA population.
- This study provided evidence for the effectiveness of baricitinib 4mg for the treatment of Chinese bDMARD-IR RA patients.

Disclosures

- Jiang N, Li M, Wang Y, Zhao J, Tian X, Zeng X have been investigators of this study; Zhu H, Li J, Xu J, Zhang Y are employees Eli Lilly and Company.
- This study was sponsored by Eli Lilly and Company.

Abbreviation

ACR: American College of Rheumatology; **ACPA:** Anti-cyclic Citrullinated Peptides Antibodies ;**AGR:** Aggregated Real-world data; **bDMARD**: Biologic Disease-modifying Antirheumatic Drug; **bDMARD-IR:** Biologic Disease-modifying Antirheumatic Drug:Inadequate Response;**CDAI**: Clinical Disease Activity Index; **CI**: Confidence interval; **CREDIT**: Chinese Registry of Rheumatoid Arthritis; **CRP**: C-reactive Protein; **cDMARDs**: Conventional Disease-Modifying Antirheumatic Drugs; **csDMARD**: Conventional Synthetic Disease-modifying Antirheumatic Drug; **DAS28**: Disease Activity Score with 28-Joint; **ESR**: Erythrocyte Sedimentation Rate; **HAQ-DI**:Health Assessment Questionnaire-disability Index; **IPD**: Individual Patient Data;**JAK**: Janus kinase;**LSM**: Least Square Mean;**NRI**: non-response imputation; **PBO:** Placebo;**RA**: rheumatoid arthritis; **RCT**: Randomized Controlled Trials; **RF:** Rheumatoid Factor;**SDAI**: Simplified Disease Activity Index; **TNFi**: Tumor Necrosis Factor Inhibitor

References

1. *Gras J. Drugs Today (Barc). 2016; 52:543-550.*
2. *Fridman JS, et al. J Immuniol. 2010; 184:5298-5307.*
3. *Genovese MC, et al. N Engl J Med. 2016;374:1243–1252.*
4. *Jin, S., et al,. Arthritis research & therapy, 2017. 19(1): p. 251*