Efficacy and safety data based on historical or pre-existing conditions at baseline for patients with active rheumatoid arthritis who were treated with baricitinib

Patients with rheumatoid arthritis (RA) have a high prevalence of comorbidities. This post-hoc analysis investigated the effect of select comorbidities (depression, osteoporosis, hepatic, cardiovascular or pulmonary disorders) on the efficacy and safety of baricitinib 4 mg once daily in patients with moderate-to-severe active RA and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

Data from the placebo-controlled periods of five baricitinib studies were pooled for baricitinib 4 mg; data for baricitinib 2 mg were not analysed due to low (n=302) patient numbers. Additional data for all baricitinib-treated patients with a median exposure of 2 years were derived from an ongoing open-label, long-term extension (LTE) study that included patients from phase II and III studies (RA-BEYOND; NCT01885078). Efficacy outcomes were evaluated at week 12 (vs placebo). Interaction of comorbidity-by-treatment was analysed using logistic regression or analysis of covariance. Safety observations up to week 16 (vs placebo) and during the LTE were summarised by the Medical Dictionary for Regulatory Activities preferred term.

Data from 1684 patients (803, baricitinib 4 mg; 881, placebo) from the placebo-controlled periods were analysed. The mean (SD) age was 52.7 (12.1) years, with only 38 (2.3%) patients aged ≥75 years; most patients (1506, 89.4%) were receiving background methotrexate, alone or in combination with another csDMARD. The numbers of patients receiving placebo and baricitinib 4 mg combined (with or without each comorbidity, respectively) were 133/1551 for depression, 247/1437 for osteoporosis, 424/1260 for hepatic disorders, 731/953 for cardiovascular disorders, and 166/1518 for pulmonary disorders. Demographic and clinical characteristics within each comorbidity subgroup were similar between patients randomised to baricitinib or placebo.

Higher proportions of patients achieved all clinical endpoints with baricitinib 4 mg than with placebo at week 12 across subgroups (table 1). Response rates in patients with or without each comorbidity who received baricitinib were generally close to overall response rates, with the exception of depression, where numerically lower response rates were observed in patients with versus without depression and overall (table 1). Responses to baricitinib versus placebo were similar between patients with or without comorbidity within each comorbidity subgroup, even for those with/without depression (p>0.1).

The safety analysis set from the placebo-controlled periods included 1683 patients (802, baricitinib; 881, placebo) with 235.2 and 246.9 patient-years of exposure (PYE) to baricitinib 4 mg or placebo, respectively. Similar proportions of patients experienced ≥1 treatment-emergent adverse events (TEAEs) between baricitinib and placebo across comorbidity subgroups (table 1). The most common TEAEs for the overall population were nasopharyngitis (5.6%, baricitinib vs 5.2%, placebo), upper respiratory tract infections (4.5% vs 3.5%), urinary tract infections (3.5% vs 2.6%) and bronchitis (2.9% vs 2.6%). Serious adverse events (SAEs) and discontinuations were infrequent, occurring at similar rates across subgroups for baricitinib and placebo. SAE and discontinuation rates for baricitinib-treated patients with/without each comorbidity were generally close to overall rates, although numerical differences were observed between patients with depression (lower rates), osteoporosis (higher rates) or pulmonary disorders (higher rates) and those without these comorbidities.

In the LTE study, safety data were available from 3439 patients with a total of 6633 PYE to baricitinib. Overall, the incidence of TEAEs, SAEs, discontinuations and reported deaths was similar between patients with or without comorbidity within each comorbidity subgroup (table 1). Further, the exposure-adjusted incidence rates for all patients were lower in the LTE than during the placebo-controlled period for all safety outcomes assessed. The numerical differences between patients with/without each comorbidity observed after 16 weeks (see above) were not observed in the LTE study.

This is the first analysis assessing the impact of select comorbidities on the efficacy and safety of baricitinib 4 mg. Limitations of this post-hoc analysis include the analysis of patient data derived from randomised clinical trials rather than real-world patient data, such that patients with certain acute or historical conditions, unstable illness, or certain laboratory abnormalities were excluded from the trials (see online supplementary text); the limited number of patients in each comorbidity subgroup and the limited duration of analyses; the non-inclusion of all known comorbidities in RA; the mix of comorbidities included in each subgroup, which could vary in severity and overall impact on patients; the inability to assess adverse events of specific interest and whether comorbidity severity improved or worsened following baricitinib treatment; and the inability to conclude on the efficacy and safety of baricitinib in patients aged ≥75 years and/or exposed to baricitinib 2 mg due to low patient numbers. Planned analyses of safety data from registries or healthcare databases in the USA and Europe are expected to address many of the current limitations.

Baricitinib 4 mg showed similar efficacy and safety during placebo-controlled and LTE observation periods regardless of the presence or absence of select comorbidities in patients with moderate-to-severe active RA and an inadequate response to csDMARDs. No trends for increased risk of safety events related to comorbidity were observed across comorbidity subgroups for baricitinib during a median exposure of 2 years. Further studies are needed to confirm the data presented, which provide a hypothesis only.

Trial registration numbers: NCT01185353, NCT01469013, NCT00902486, NCT01710358 and NCT01721057.
Table 1  Efficacy and safety data reported by select comorbidities in patients treated with baricitinib or placebo*

| Comorbidity          | Baricitinib 4 mg | Placebo |
|----------------------|------------------|---------|
| **Efficacy outcomes at week 12** |                  |         |
| Depression No depression | 64  | 69   |
| Osteoporosis No osteoporosis | 739 | 812   |
| Hepatic disorders No hepatic disorders | 222 | 202 |
| CV disorders No CV disorders | 581 | 350 |
| Pulmonary disorders No pulmonary disorders | 350 | 450 |
| Overall | 453 | 77  |
| ACR20 response (%)† | 59.4 | 31.9 |
| ACR50 response (%)† | 34.4 | 8.7 |
| DAS 28-hsCRP ≤3.2 response (%)† | 31.3 | 13.0 |
| Change in HAQ-DI‡ | −0.46 | −0.20 |
| **Safety outcomes at week 16** |                  |         |
| Any TEAE, n (%), (EAIR) | 45 (70.3), (246) | 45 (82.6), (301) |
| SAE, n (%), (EAIR) | 0, (0.0) | 0, (0.0) |
| Discontinuation due to AEs, n (%), (EAIR) | 1 (1.6), (5.5) | 1 (1.4), (5.3) |
| Deaths, n (%), (EAIR) | 0, (0.0) | 0, (0.0) |
| ACR20 response (%)† | 31.9 | 31.9 |
| ACR50 response (%)† | 8.7 | 8.7 |
| DAS 28-hsCRP ≤3.2 response (%)† | 13.0 | 13.0 |
| Change in HAQ-DI‡ | −0.26 | −0.26 |
| **Safety outcomes after median exposure of 2 years** |                  |         |
| Any TEAE, n (%), (EAIR) | 57 (82.6), (301) | 57 (82.6), (301) |
| SAE, n (%), (EAIR) | 6 (8.7), (31.7) | 4 (6.9), (31.7) |
| Discontinuation due to AEs, n (%), (EAIR) | 3 (4.3), (15.9) | 1 (1.4), (5.3) |
| Deaths, n (%), (EAIR) | 0, (0.0) | 0, (0.0) |

*Depression and osteoporosis data are presented as numbers, while hepatic disorders, CV disorders, and pulmonary disorders data are presented as percentages. ACR20, ACR50, and DAS 28-hsCRP ≤3.2 response data are presented as percentages. HAQ-DI change data are presented as numbers. TEAE, any treatment-emergent adverse event; SAE, serious adverse event.

†Expressed as a percentage of the total number of patients treated with the respective treatment in each category.

‡Expressed as a change from baseline.

§Expressed as a change from week 12.

Continued
Comorbidities and associated terms are based on the Medical Dictionary for Regulatory Activities classification system. Terms for depression included depressed mood, depression postoperative, depression, depressive symptoms, dysthmic disorder, major depression, suicidal ideation and suicide attempt. Terms for osteoporosis included low bone density (bone density decreased), non-traumatic bone fracture (osteoporotic fracture), osteoarthritis, osteoporosis postmenopausal, osteoporosis and senile osteoporosis. Terms for hepatic disorders included alanine aminotransferase increased, aspartate aminotransferase increased, biliary cirrhosis primary, blood alkaline phosphatase increased, cholestasis, chronic hepatitis, drug-induced liver injury, gamma-glutamyltransferase increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hepatic lesion, hepatic steatosis, hepatitis, hepatitis acute, hepatitis toxic, hepatomegaly, hypertransaminaseemia, hypoalbuminemia, jaundice, liver disorder, liver function test abnormal, liver injury, liver operation, non-alcoholic steatohepatitis, serum hepatitis B virus core antibody positive, serum hepatitis B virus surface antibody positive, spider nevus, transaminases increased and varices oesophageal. Terms for cardiovascular disorders included acute myocardial infarction, blood cholesterol increased, blood glucose abnormal, blood glucose increased, cerebral infarction, cerebrovascular accident, coronary artery bypass, diabetes mellitus, diabetes mellitus inadequate control, diabetic ketoacidosis, essential hypertension, gestational diabetes, glucose tolerance impaired, hypercholesterolaemia, hyperglycaemia, hyperlipidaemia, hypertension, hypertensive cardiomyopathy, hypertensive heart disease, intermittent claudication, ischaemic stroke, labile hypertension, lacunar infarction, low-density lipoprotein increased, myocardial infarction, peripheral arterial occlusive disease, peripheral arterial stenosis, subarachnoid haemorrhage, subdural haematoma, systolic hypertension and transient ischaemic attack. Terms for pulmonary disorders included allergic bronchitis, apnoea, asthma, aspirin-exacerbated respiratory disease, asthma, asthma exercise-induced, atelectasis, bronchial hyper-reactivity, bronchitis, bronchiolitis, bronchitis chronic, bronchospasm, bullous lung disease, chronic obstructive pulmonary disease, cor pulmonale chronic, diffuse panbronchiolitis, dyspnoea, dyspnoea exertional, emphysema, idiopathic pulmonary disease, infantile asthma, interstitial lung disease, Langerhans cell histiocytosis, lung consoladation, lung cyst, obstructive airways disorder, pneumocystis, pneumonia, pulmonary bulla and pulmonary fibrosis. The number of patients with idiopathic pulmonary disease, interstitial lung disease or pulmonary fibrosis was low (6 and 8 patients for baricitinib 4 mg and placebo respectively); thus, the impact of these conditions on baricitinib treatment outcomes cannot be concluded with certainty.

*Efficacy outcomes were assessed at week 12 for baricitinib and placebo; safety outcomes were recorded from baseline to week 16 for baricitinib and placebo in the randomised controlled trials and for all patients receiving baricitinib after a median exposure of 2 years in the long-term extension study.

†Percentage of patients achieving ACR20, ACR50 and DAS 28-4sCRP ≤3.2.

‡Least squares mean changes in HAQ-DI scores from baseline to week 12; negative changes indicate improvement from baseline.

|| Discontinuation due to AEs, n (%), (EAIR) | Depression | No depression | Osteoporosis | No osteoporosis | Hepatic disorders | No hepatic disorders | CV disorders | No CV disorders | Pulmonary disorders | No pulmonary disorders | Overall |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 36 (10.5), (5.8) | 283 (9.1), (4.7) | 71 (14.2), (7.3) | 248 (8.4), (4.4) | 93 (11.5), (5.9) | 226 (8.6), (4.5) | 173 (11.3), (5.7) | 146 (7.7), (4.0) | 35 (9.4), (4.7) | 284 (9.3), (4.8) | 319 (9.3), (4.8) |
| 3 (0.9), (0.5) | 10 (0.3), (0.2) | 7 (1.4), (0.7) | 6 (0.2), (0.1) | 1 (0.1), (0.0) | 12 (0.5), (0.2) | 9 (0.6), (0.3) | 4 (0.2), (0.1) | 4 (1.0), (0.5) | 9 (0.3), (0.2) | 13 (0.4), (0.2) |

Table 1 Continued
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Handling editor Josef S Smolen

Acknowledgements The authors would like to acknowledge Ioannis Nikas, PhD, and Sue Chambers, PhD (Rx Communications, Mold, UK) for medical writing assistance during the preparation of this research letter, funded by Eli Lilly and Company.

Contributors All authors contributed substantially to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work; drafted the work or revised it critically for important intellectual content; gave their final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This study was funded by Eli Lilly and Company and Incyte Corporation. IdiT, VR, FD and SW are employees of Eli Lilly and Company and, together with the other authors, were involved in the study design; in the collection, analysis, and interpretation of the data; in the writing of the report; and in the decision to submit the paper for publication.

Competing interests BC reports grants and personal fees from Merck and Pfizer, and personal fees from AbbVie, BMS, Janssen, Eli Lilly, Roche Chugai, Sanofi and UCB, outside the submitted work. AB reports grants and personal fees from Eli Lilly, during the conduct of the study, and grants from Pfizer, AbbVie, MSD and BMS, grants and personal fees from Novartis and Nordic, and personal fees from UCB, Celltrion, Kern Pharma, Sanofi and Sandoz, outside the submitted work. HP-T reports personal fees from AbbVie, Chugai, Janssen Cilag, Eli Lilly, Novartis, Roche, Sandoz Heaxal and Sanofi Aventis, outside the submitted work. MD reports grants and personal fees from Eli Lilly, Pfizer, AbbVie and UCB, during the conduct of the study. VR is a minor shareholder of Eli Lilly and Company. PSP, JZ, IdiT, FD and SW report no conflicts of interest.

Patient consent Obtained.

Ethics approval All studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Studies were approved by the following review boards: NCT01469013: Parexel #205204; NCT01185353: Schulman Associates IRB, IRB #10-5255-0; NCT00902486: Copernicus Group IRB #RAP1-09-143; NCT01710358 (RA-BUILD): Quorum Review IRB #27257; NCT01721057 (RA-BUILD): Quorum Review IRB #27258. In addition, studies were approved by each participating centre’s institutional review board or ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data will not be shared as they are proprietary information.

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Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2018-214261).

To cite Combe B, Balsa A, Sarzi-Puttini P, et al. Ann Rheum Dis 2019;78:1135–1138.

Received 10 August 2018
Revised 7 February 2019
Accepted 8 February 2019
Published Online First 6 March 2019

Ann Rheum Dis 2019;78:1135–1138. doi:10.1136/annrheumdis-2018-214261

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