TOFACITINIB IN THE TREATMENT OF SEVERE AND REFRACTORY BEHÇET’S DISEASE: A SINGLE-CENTRE EXPERIENCE IN CHINA

J. Liu¹, L. Sun¹, F. Zhang¹, W. Zheng¹. ¹Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Department of Rheumatology and Clinical Immunology, Key Laboratory of Rheumatology and Clinical Immunology, National Clinical Research Center for Dermatologic and Infectious Diseases (NCRC-DID), Beijing, China

Background: Small-molecule JAK inhibitors have succeeded in the treatment of rheumatoid arthritis, psoriasis, and inflammatory bowel disease¹. Tofacitinib is under investigation for various autoimmune diseases, but its effectiveness on Behçet’s disease (BD) has not been demonstrated.

Objectives: We aimed to investigate the efficacy and safety of Tofacitinib in the treatment of severe and refractory BD.

Methods: We retrospecively analyzed the efficacy and safety profile of Tofacitinib in treating severe and refractory BD patients in our hospital from 2017 to 2020.

Results: Thirty BD patients (7 males and 6 females) were enrolled, with a mean age and median course of 40.6±14.7 years and 84 months (60,132). Vascular/cardiac, gastrointestinal, and articular involvement were present in 5, 6, and 2 patients, respectively. Three patients had multiple arterial stenosis or occlusion, two presented with aortic root dilation with aortic valve regurgitation, and one experienced perivalvular leakage (PVL). All the six patients with gastrointestinal involvement had multiple episodes of ileocecal and colon ulcers, intestinal bleed, and three had anastomotic ulcers or leaks.

All the patients had received high-dose glucocorticoids and immunosuppressants before tofacitinib therapy, they displayed poor response with evidence of disease progression; furthermore, three patients with gastrointestinal involvement and one patient with polyarthritis had failed anti-TNF antibody treatment. They were then treated with Tofacitinib, 5mg twice daily, with background glucocorticoids and immunosuppressants, for a median of 6 months (range 4 to 19).

After a median follow-up of 7 (5, 19) months, the ESR and CRP level decreased significantly (21(8, 50) mm/h vs 8(3, 19.5) mm/h, P<0.01, and 25(8, 55, 49.5) mg/L vs 18(9.44, 6.65) mg/L, P<0.01, respectively). All patients with vascular/cardiac and articular involvement achieved clinical improvement. Vascular lesions of three patients were radiologically stable, no progressive aneurysm or PVL was observed. Two patients with intestinal ulcers revealed complete mucosal healing; the other three had sustained elevation of ESR and CRP. Active mucosal ulcers, recurrent bleeding, or fistula formation. The dose of corticosteroids was tapered in six cases (46.2%), furthermore, the number of immunosuppressants lessened in seven cases. However, two patients had herpes zoster infection during follow up, while being treated with five to six immunosuppressants in addition to Tofacitinib for refractory intestinal ulcers.

Conclusion: Our study suggests that Tofacitinib is effective for the treatment of vascular and articular BD; given the limited data, its therapeutic effect on gastrointestinal BD could not be validated. We have to be cautious of infectious risk for severely immunocompromised patients. Further large-scale prospective studies are warranted to confirm the therapeutic potential of JAK inhibitors in BD patients.

References:


Disclosure of Interests: None declared.

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SAFETY AND EFFICACY OF SUBCUTANEOUS TOCILIZUMAB IN SYSTEMIC SCLEROSIS: RESULTS FROM THE OPEN-LABEL PERIOD OF THE PHASE 3 FOCUSED TRIAL

D. Khanna,1 C. F. J. Lin,2 H. Spotswood,3 J. Siegel,4 D. Furst,4 C. Denton.4
1University of Michigan, Ann Arbor, United States of America; 2Genentech, South San Francisco, United States of America; 3Roche Products Ltd, Weilwyn Garden City United Kingdom; 4University of California, Los Angeles, Los Angeles, United States of America; 5University College London, London, United Kingdom

Background: The anti-interleukin-6 (IL-6) receptor-α antibody tocilizumab (TCZ) demonstrated skin score improvement and forced vital capacity (FVC) preservation in patients with systemic sclerosis (SSc) in a phase 2 randomized controlled trial.1,2 Data from the 48-week, double-blind (DB), placebo (PBO)-controlled period of the focusSced phase 3 trial were previously presented,3 and open-label (OL) data up to week 96 are presented here.

Objectives: To assess the long-term safety and efficacy of TCZ in SSc patients.

Methods: Adult patients with active SSc (≤60-month duration, modified Rodnan skin score [mRSS] 10-35), and elevated acute-phase reactants treated with PBO or TCZ in the DB period received OL TCZ 162 mg SC weekly from weeks 48 to 96 in the OL period (PBO→OL TCZ and TCZ→OL TCZ, respectively). Exploratory analysis of data up to week 96 included no formal statistical analyses. Changes in mRSS and percent predicted FVC (ppFVC) were assessed. Results: Overall, 92/105 TCZ (88%) and 89/107 PBO (83%) patients entered the OL TCZ treatment period at week 48, and 85/105→OL TCZ (81%) and 82/107 PBO→OL TCZ (77%) patients completed treatment up to week 96. Continued decline in mRSS was observed in the OL period for PBO→TCZ and TCZ→OL TCZ patients (Table). Change in ppFVC for patients who switched from PBO to TCZ (PBO→TCZ) was comparable between weeks 48 and 96 (OL period) to the change in patients who received TCZ from BL to week 48 in the DB period (Table). Rates (95% CI) of serious adverse events from weeks 48 to 96 were 15.8 (8.6, 26.5) per 100 PY for TCZ and 9.3 (5.4) per 100 PY for PBO. Change in ppFVC for patients who switched from PBO to TCZ (PBO→TCZ) was comparable between weeks 48 and 96 (OL period) to the change in patients who received TCZ from BL to week 48 in the DB period (Table). Rates (95% CI) of serious adverse events from weeks 48 to 96 were 15.8 (8.6, 26.5) per 100 PY for TCZ and 9.3 (5.4) per 100 PY for PBO. Change in ppFVC for patients who switched from PBO to TCZ (PBO→TCZ) was comparable between weeks 48 and 96 (OL period) to the change in patients who received TCZ from BL to week 48 in the DB period (Table). Rates (95% CI) of serious adverse events from weeks 48 to 96 were 15.8 (8.6, 26.5) per 100 PY for TCZ and 9.3 (5.4) per 100 PY for PBO.

Conclusion: Although OL data have to be interpreted with caution, results from OL TCZ treatment show numeric improvements in mRSS and FVC preservation similar to those of the DB period, with a beneficial effect on trajectory of FVC decline in patients who switched from PBO to TCZ. Long-term safety results were consistent with the known safety profile of TCZ, and no new or unexpected events were observed.

References:

Disclosure of Interests: Dinesh Khanna Shareholder of: Eisai, Grant/research support from: NIH NIADDK, NIH NIAMS, Consultant of: Acceleron, Actelion, Bayer, BMS, Boehringer-Ingelheim, Corbus, Galapagos, Genentech/Roche, GSK, Mitsubishi Tanab, Sanofi-Aventis/Genzyme, UCB Pharma, Celia J. F. Lin Employee of: Genentech, Helen Spotswood Shareholder of: Roche Products Ltd, Employee of: Roche Products Ltd, Jeff Siegel Employee of: Genentech, Daniel Furst Grant/research support from: AbbVie, Actelion, Amgen, BMS, Corbus Pharmaceuticals, the National Institutes of Health, Novartis, Pfizer, and Roche/Genentech, Consultant of: AbbVie, Actelion, Amgen, BMS, Cytokine Therapeutics, Corbus Pharmaceuticals, the National Institutes of Health, Novartis, Pfizer, and Roche/Genentech, Speakers bureau: CMC Connect (McCann Health Company), Christopher Denton Grant/research support from: GlaxoSmithKline, CSL Behring, and Inventiva, Consultant of: Medscape, Roche-Genentech, Actelion, GlaxoSmithKline, Sanofi Aventis, Inventiva, CSL Behring, Boehringer Ingelheim, Corbus Pharmaceuticals, Acceleron, Curzion and Bayer

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SAFETY, TARGET ENGAGEMENT, AND INITIAL EFFICACY OF AVID200, A FIRST-IN-CLASS POTENT AND ISOFORM-SELECTIVE INHIBITOR OF TGF-BETA 1 AND 3, IN PATIENTS WITH DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS (DCSSC): A PHASE 1 DOSE ESCALATION STUDY

R. Loytay1, R. Spiera1, R. Domsic1, A. Papazoglou1, C. Ligori1, C. M. Zinger More1, J. F. Denis2, M. Davis3, T. Grusso1, G. Tremblay4, M. O’Connor Mccourt5, S. Sinclair5, J. Delara5, K. Alvarado5, D. Wood5, P. Nadler5, E. Volkmann6, University of Pittsburgh, Pittsburgh, United States of America; 2Hospital for Special Surgery, New York City, United States of America; 3University of Pennsylvania, Philadelphia, United States of America; 4Forbis, Montréal, Canada; 5Forbis, Austin, United States of America; 6UCLA, Los Angeles, University of States of America

Background: AVID200 is a novel, potent TGF-beta receptor ectodomain-based trap designed to selectively neutralize TGF-beta 1 and 3. These two isoforms have been implicated as central mediators of the pathogenesis of systemic sclerosis (SSc). AVID200 avoids inhibition of TGF-beta 2, the isoform that supports normal cardiac function and hematopoiesis.

Objectives: This first-in-human study (AVID200-01: NCT03831438) is a Phase 1, open label, multicenter, cohort dose-escalation trial designed to evaluate safety, tolerability, pharmacokinetic (PK) profile, pharmacodynamic (PD) effects, target engagement, and preliminary efficacy in patients with diffuse cutaneous SSc (dcSSc).

Methods: Eligible patients must have dcSSc of ≤5 years (y) duration and a modified Rodnan Skin Score (mRSS) ≥15. AVID200 at dose levels of 1, 3, 9, or 15 mg/kg IV is administered every 2 weeks (Q2W) for 6 weeks (3 doses). Patients tolerating dosing and who have not experienced disease worsening during the initial Treatment Period may receive up to 6 additional doses Q2W (Extension Period). The ability of AVID200 to selectively sequester its target is assessed in plasma by TGF-beta quantification per ELISA and a cell-based functional read-out. Expression of biomarkers of TGF-beta inhibition and genes correlating with MRSS are assessed.

Table. Change in Efficacy From Baseline

<table>
<thead>
<tr>
<th></th>
<th>Baseline to Week 48</th>
<th>Baseline to Week 96</th>
<th>Week 48 to Week 96</th>
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<tbody>
<tr>
<td></td>
<td>PBO</td>
<td>TCZ</td>
<td>PBO→OL TCZ</td>
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<tr>
<td>n RSS, mean (95% CI)‡</td>
<td>–5.3 (–6.9, –3.7)</td>
<td>–6.7 (–8.0, –5.4)</td>
<td>–8.4 (–10.0, –6.8)</td>
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<tr>
<td>n = 92</td>
<td>n = 89</td>
<td>n = 92</td>
<td>n = 89</td>
</tr>
<tr>
<td>PPVFC, mean (95% CI)median</td>
<td>–4.1 (–5.8, –2.4)</td>
<td>–2.0 (–1.6, –1.2)</td>
<td>–3.3 (–5.1, –1.5)</td>
</tr>
<tr>
<td>n = 92</td>
<td>n = 94</td>
<td>n = 97</td>
<td>n = 79</td>
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<tr>
<td>15/91</td>
<td>5/93</td>
<td>14/79 (17.7)</td>
<td>11/84 (13.1)</td>
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<td>(16.5) (5.4)</td>
<td>(5.4)</td>
<td>(16.5) (17.7)</td>
<td>(16.5) (13.1)</td>
</tr>
<tr>
<td>Improvement in PPVFC, n/N (%)‡</td>
<td>26/91 (28.6) (46.2)</td>
<td>22/79 (27.8) (41.7)</td>
<td>35/84 (NA)</td>
</tr>
</tbody>
</table>

‡Observed data. NA, not assessed.