THU0326

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

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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 diseases², 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 retrospectively analyzed the efficacy and safety profile of Tofacitinib in treating severe and refractory BD patients in our hospital from 2017 to 2020.

Results: Thirteen 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 presented 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(5.85, 49.5) mg/L vs 1.89(0.44, 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.

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Scleroderma, myositis and related syndromes

THU0327

EFFECT OF IMMUNOSUPPRESSIVE MEDICATION ON GASTRO-INTESTINAL INVOLVEMENT IN SYSTEMIC SCLEROSIS PATIENTS STRATIFIED FOR DISEASE DURATION.

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Background: Gastrointestinal tract (GIT) involvement is associated with high morbidity in systemic sclerosis (SSc) but the data on its impact from unselected and well characterized SSc cohorts are scarce. Currently, the effect of immunosuppressive (IS) treatment on GIT involvement is largely unknown.

Objectives: To evaluate the severity and worsening of GIT involvement in two prospective SSc cohorts. To assess factors associated with severity of GIT involvement, stratified for disease duration. To evaluate effect of IS treatment on worsening of GIT involvement.

Methods: All SSc patients fulfilling the 2013 SSc classification criteria from two SSc cohorts were evaluated. Incident SSc was defined as disease duration since first symptom non-Raynaud < 24 months at first presentation. GIT involvement was assessed by the UCLA GIT 2.0 score at baseline and after one year to assess worsening of GIT involvement. Worsening was defined as change > minimal clinical important difference for total score and for each of the seven subdomains. GIT involvement was defined as present if the patients reported symptoms resulting in a score of ≥0.01 and was segregated into mild ≥0.01 (<0.5 or for fecal incontinence and distention/bloating <1.01), moderate (≥0.5 or for fecal incontinence and distention/bloating ≥1.01) or severe GI symptoms (> 1.01 or for distention/bloating > 1.61 or for fecal soiling > 2.01). Logistic regression was applied to identify risk factors associated with GIT involvement at baseline. The effect of IS treatment on worsening on each of the subdomains after one year was evaluated with logistic regression, with adjustment for baseline disease duration and severity.

Results: In total, 834 SSc patients were included; 236 (28%) had incident disease (table 1). Incident cases (IC) showed comparable severity of GIT involvement compared to non-incident cases (NIC) except for significantly less severe reflux and distention/bloating (figure 1). Logistic regression showed female sex (OR 8.5(1.1-36.01)) and smoking (OR 2.9(1.2-7.3)) to be associated with GIT severity at baseline in IC; in NIC anti-centromere antibody (OR 1.7(1.3-2.2)) was additionally associated with GIT severity. The use of IS at baseline did not associate with GI severity at baseline. In total n = 685 (82% never had IS treatment (83% NIC, 81% IC); of these 258 (38%) started with IS after baseline assessment (52% IC, 32% NIC, $p=0.02$). When comparing change of GIT involvement after one year between those who started IS and those who did not, worsening of GI symptoms occurred more frequently in patients who started IS treatment (figure 2), but notably, patients in this group were also more frequently anti-topoisomerase positive, had ILD, and diffuse disease subset compared to the patients without IS treatment; age and sex were comparable. In the logistic regression with adjustment for disease duration and severity, there were no significant associations between IS treatment and worsening on GIT involvement.

Conclusion: Regardless disease duration, about 1/3 of all SSc patients had moderate-severe GIT involvement. Disease duration and treatment initiation with IS did not have a significant influence on worsening of GIT involvement.

Table:

Baseline characteristics

	Non-inception cohort (n=598)	Inception cohort (n=236)
Female, n(%)	504 (85)	180 (76)
Age, mean(SD)	55 (13)	56 (14)
Disease duration non Raynaud-Phenomenon, median (IQR)	8.8 (4.8-14.4)	0.7 (0.3-1.2)
Diffuse cutaneous subset, n(%)	119 (20)	67 (28)
Interstitial lung disease, n(%)	233 (39)	71 (30)
Anti-centromere, n(%)	296 (50)	96 (41)
Immunosuppressive treatment at baseline, n(%)	102 (17)	44 (19)
Duration of treatment at baseline in years, mean (SD)	4.1 (4.8)	1.2 (2.9)
Methotrexate, n(%)	54 (9)	24 (10)
Mycophenolate mofetil, n(%)	25 (4)	13 (6)
Hydroxychloroquine, n(%)	20 (3)	7 (3)
Cyclofosamide, n(%)	1 (1)	10 (4)
Azathioprine, n(%)	11 (2)	2 (1)
Corticosteroids, n(%)	58 (10)	27 (11)

Figure 1. Severity of GI involvement per subdomain for the non-inception cohort and the inception cohort at baseline.

Figure 2. Percentage of progressors in inception cohort versus percentage of progressors in non-inception cohort after one year of follow-up stratified for immunosuppressive treatment (n=250 non-inception cohort, n=106 inception cohort).

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THU0328

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

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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 focussed phase 3 trial were previously presented,³ and open-label (OL) data up to week 96 are presented herein.

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 $\rightarrow$ OL TCZ and TCZ $\rightarrow$ 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 TCZ $\rightarrow$ OL TCZ (81%) and 82/107 PBO $\rightarrow$ OL TCZ (77%) patients completed treatment up to week 96. Continued decline in mRSS was observed in the OL period for PBO $\rightarrow$ OL TCZ and TCZ $\rightarrow$ OL TCZ patients (Table). Change in ppFVC for patients who switched from PBO to TCZ (PBO $\rightarrow$ OL 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 $\rightarrow$ OL TCZ patients, 14.8 (7.9, 25.3) per 100 PY for PBO $\rightarrow$ OL TCZ patients, and 15.4 (11.0, 20.9) for all TCZ exposure over 96 weeks (n = 193). Rates (95% CI) of serious infections were 2.3 (0.3, 8.1) per 100 PY for TCZ $\rightarrow$ OL TCZ patients, 3.4 (0.7, 10.0) per 100 PY for PBO $\rightarrow$ OL TCZ patients, and 3.0 (1.3, 5.9) for all TCZ exposure over 96 weeks. One death occurred during the OL period in each arm.

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.

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THU0329

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

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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

	Baseline to Week 48		Baseline to Week 96		Week 48 to Week 96	
	PBO	TCZ	PBO $\rightarrow$ OL TCZ	TCZ $\rightarrow$ OL TCZ	PBO $\rightarrow$ OL TCZ	TCZ $\rightarrow$ OL TCZ
mRSS, mean (95% CI) ^a	-5.3 (-6.9, -3.7) n = 92	-6.7 (-8.0, -5.4) n = 97	-8.4 (-10.0, -6.8) n = 83	-9.6 (-10.9, -8.4) n = 85	-2.5 (-3.3, -1.6) n = 82	-2.3 (-3.2, -1.5) n = 85
ppFVC, mean (95% CI) [median]	-4.1 (-5.8, -2.4) [-3.9] n = 92	-0.2 (-1.6, 1.2) [-0.7] n = 94	-3.3 (-5.1, -1.5) [-3.1] n = 79	-0.5 (-2.4, 1.3) [-1.4] n = 84	0.6 (-0.7, 1.9) [0.3] n = 78	-0.3 (-1.7, 1.1) [0.0] n = 82
Decline in ppFVC $\geq 10\%$, n/N (%) ^a	15/91 (16.5)	5/93 (5.4)	14/79 (17.7)	11/84 (13.1)	NA	NA
Improvement in ppFVC, n/N (%) ^a	26/91 (28.6)	43/93 (46.2)	22/79 (27.8)	35/84 (41.7)	NA	NA

^aObserved data. NA, not assessed.