OP0103 IDENTIFICATION OF OPTIMAL SUBCUTANEOUS DOSES OF TOCILIZUMAB IN CHILDREN WITH SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

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Background: Efficacy and safety of intravenous (IV) tocilizumab (TCZ) were demonstrated in patients (pts) with systemic juvenile idiopathic arthritis (sJIA) in the phase 3 TENDER study[1] (WA18221). Study WA28118 (ClinicalTrials.gov, NCT01904292) investigated dosing regimens of subcutaneous (SC) TCZ in pts with sJIA by bridging to IV TCZ data to identify the optimal SC regimen.
Objectives: To characterise the pharmacokinetics (PK), pharmacodynamics (PD), and safety of TCZ SC in pts with sJIA; efficacy was an exploratory objective.
Methods: This phase 1b multicenter, open-label study evaluated PK, PD, and safety of TCZ SC in pts aged 1–17 years with sJIA and inadequate response to glucocorticoids and nonsteroidal anti-inflammatory drugs. Interim analysis (IA) was conducted after 24 pts had received TCZ SC for 14 weeks. Pts could be either TCZ-naive or switch from TCZ IV to SC at baseline. TCZ SC was administered for 52 weeks according to body weight:<30 kg, either 162 mg every 10 days (before IA) or 162 mg every 2 weeks (Q2W, after IA); ≥30 kg, 162 mg every week (QW).
Results: Among enrolled pts (n=51), 25 weighed <30 kg (8 before and 17 after IA) and 26 weighed ≥30 kg. Twenty-six pts (51%) were TCZ naive and 25 (49%) switched from TCZ IV. Median steady state C_{min} was similar for pts<30 kg receiving TCZ 162 mg Q2W and those ≥30 kg receiving TCZ 162 mg QW, and the range largely overlapped (table 1). More than 95% (49/51) of pts treated with TCZ SC had model-computed steady state C_{min} higher than the 5th percentile achieved with TCZ IV. Median and range of AUC_{2weeks} were similar for both weight groups (table 1). Changes in interleukin-6, C-reactive protein, and erythrocyte sedimentation rate were similar for both weight groups. Most pts had ≥1 adverse event (AE; n=50; 98%). Injection site reactions (ISRs) occurred in 21 pts (41%); most were mild and none led to treatment interruption/withdrawal. AE rate was 1200.3/100 patient-years (PY) (909.3/100 PY excluding ISRs). The most common AEs were viral upper respiratory tract infection (13; 25.5%), neutropenia (13; 25.5%), and cough (12; 23.5%). Nine serious AEs occurred in 7 pts (13.7%; 19.3/100 PY); 5 were infections, all in the <30 kg group. Two deaths occurred, both in the <30 kg group. Median Juvenile Arthritis Disease Activity Score-71 improved (decreased) from baseline to week 52 for TCZ-naive pts (<30 kg, –13.9; ≥30 kg, –12.4) and was maintained or improved further for pts who switched from TCZ IV (<30 kg, –0.7; ≥30 kg –0.2).

Abstract OP0103 – Table 1

	TCZ SC (WA28118)		TCZ IV (WA18221)	
	<30 kg TCZ 162 mg Q2W n = 25	≥30 kg TCZ 162 mg QW n = 26	<30 kg TCZ 12 mg/kg Q2W n = 46	≥30 kg TCZ 8 mg/kg Q2W n = 43
Model-computed steady state PK parameters, median (range)				
$C_{min,ss}$ µg/mL	64.2 (16.6-135.9)	72.4 (19.5-157.8)	65.9 (19.0-135.5)	70.7 (5.3-126.6)
$C_{max,ss}$ µg/mL	126.6 (51.7-265.8)	89.8 (26.4-190.2)	274.4 (148.8-444.0)	253.0 (119.6-404.3)
$AUC_{2weeks,ss}$ µg/mL×day	1298 (539-2792)	1154 (334-2370)	1734 (840-2712)	1631 (526-2779)

Conclusions: A PK-based strategy successfully bridged TCZ SC to TCZ IV in pts with sJIA. Dosing regimens of 162 mg Q2W in pts<30 kg and 162 mg QW in pts≥30 kg provided adequate exposure to support efficacy comparable to that of TCZ IV. Except for ISRs, safety was consistent with the known safety profile of TCZ IV in sJIA.

REFERENCE:

[1] De Benedetti F, et al. N Engl J Med 2012;367:2385–2395.

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WEDNESDAY, 13 JUNE 2018: Burning bones

OP0104 ANTIBODIES AGAINST CARBAMYLATED PROTEINS ARE INVOLVED IN OSTEOCLASTOGENESIS BY INDUCING RANKL EXPRESSION IN OSTEOBLASTS IN VITRO

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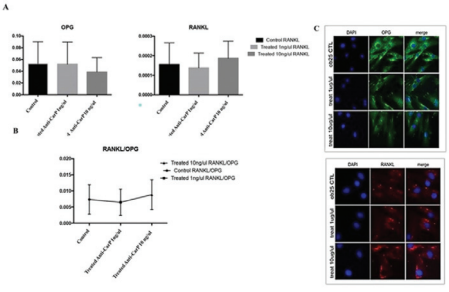
Background: Citrullinated peptide are one of the main target of immune response in Rheumatoid Arthritis (RA) and antibodies to citrullinated peptides (ACPA) are involved in bone resorption. One of the target antigens – citrullinated vimentin – is expressed on the surface of osteoclast precursors where it can bind the antibodies starting the differentiation in mature osteoclast. Moreover, recent data demonstrated that serum levels of receptor activator of nuclear factor-κB ligand (RANKL) are higher in ACPA-positive RA patients. RANKL is the main osteoblast-derived cytokine inducing osteoclastogenesis. Antibodies directed against carbamylated proteins (Anti-CarP) have been recently described in RA patients with Rheumatoid Arthritis. The effect of anti-CarP on bone resorption has not been yet addressed.
Objectives: The aim of the study was to investigate *in vitro* the effect of anti-CarP on Osteoprotegerin (OPG) and RANK ligand (RANKL) production in osteoblast cultures.
Methods: Anti-CarP were investigated by ELISA in the sera of 88 RA patients using carbamylated fetal calf serum (CarFCS) and non-modified FCS as antigens. Anti-CarFCS were purified from the sera of 3 RA patients who tested highly positive for anti-CarP. Osteoblasts were isolated from the femoral head of 3 patients undergoing total hip arthroplasty and cultured in three different conditions – 1 ng/ml of anti-CarFCS, 10 ng/ml of anti-CarFCS or control medium for 4–6 days, until confluence. RNA was extracted from cell lysates and OPG and RANKL mRNA expression was analysed by Real-time PCR. Moreover, OPG and RANK expression was investigated by immunofluorescence on treated and non-treated cells. differences were determined either with two-way repeated measures analysis of variance (ANOVA) with Bonferroni's multiple comparison test, using Prism 5.0 software. A p value<0.05 was considered significant.
Results: In osteoblast cultures, anti-CarFCS decreased the expression of OPG and increased the expression of RANKL in a dose-dependent manner, leading to an increase in RANKL/OPG ratio (figure 1A and 1B). The result was confirmed by the immunofluorescence analysis demonstrating the subcellular co-location of OPG and RANKL in osteoblast cultures (figure 1C).



Abstract OP0104 – Figure 1. Expression of mRNA for RANKL and OPG (A) and RANKL/OPG ratio (B) in osteoblast cultures treated with anti-CarFCS; sub-cellular location of RANKL and osteoprotegerin in osteoblasts' cultures (C).

Conclusions: The results of the study confirm that anti-CarFCS can be detected in nearly 40% of RA patients. The increase of RANKL/OPG ratio in the osteoblast cultures treated with anti-CarFCS suggests an effect of such autoantibodies on osteoclastogenesis and osteoclasts activity, supporting their possible involvement in the development of bone erosions.

Disclosure of Interest: None declared
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