102. TOCILIZUMB DID NOT SIGNIFICANTLY INCREASE SERUM CHOLESTEROL LEVELS IN HEALTHY SUBJECTS

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Background: Cardiovascular (CV) risk is increased among patients with RA and is comparable to that observed for patients with type 2 diabetes, largely driven by the high systemic inflammatory burden associated with RA. The heightened inflammatory state in RA is thought to account for a lipid paradox, in which serum cholesterol is inversely related to inflammation in patients with untreated RA. Suppression of disease activity and inflammation with RA therapies, including tocilizumab (TCZ), has been associated with increases in serum lipid levels in RA patients, and is thought to reflect a normalization of lipid levels to those seen in the general population. To ascertain what impact TCZ may have on cholesterol levels in the absence of inflammation, the impact of therapeutic and supra-therapeutic doses of TCZ on cholesterol levels in healthy subjects were examined.
Methods: This study was conducted as a single dose, randomized, double-blind, placebo-controlled, parallel group study investigating therapeutic and a supra-therapeutic doses of TCZ. Healthy subjects were randomized 1:1:1 to placebo (PBO), TCZ 10 mg/kg, or TCZ 20 mg/kg, and received a single i.v. dose on Day 1. The dose of 10 mg/kg, given as a single dose, was selected because this dose mimics the

102 TABLE 1. Summary of change from baseline of cholesterol levels by study treatment

Change from BL, mean (S.D.), mmol/l	Scheduled visit (day)									
	1	2	3	5	8	11	15	22	29	50
TCh										
PBO ($n=29$)	–0.16 (0.36)	–0.01 (0.41)	0.19 (0.44)	–0.04 (0.48)	0.07 (0.57)	–0.22 (0.51)	0.11 (0.72)	–0.04 (0.60)	–0.07 (0.60)	–0.15 (0.53)
TCZ 10 mg/kg ($n=30$)	–0.17 (0.27)	0.02 (0.33)	0.19 (0.38)	0.11 (0.35)	0.30 (0.37)	0.22 (0.38)	0.16 (0.51)	0.05 (0.49)	0.13 (0.47)	–0.10 (0.39)
TCZ 20 mg/kg ($n=31$)	–0.19 (0.24)	–0.03 (0.28)	0.16 (0.42)	0.08 (0.47)	0.31 (0.47)	0.21 (0.47)	0.39 (0.56)	0.22 (0.63)	0.25 (0.55)	0.22 (0.47)
HDL										
PBO ($n=29$)	–0.07 (0.24)	–0.05 (0.23)	–0.01 (0.22)	–0.02 (0.22)	0.02 (0.25)	–0.04 (0.25)	0.06 (0.26)	0.02 (0.25)	0.02 (0.20)	0.00 (0.19)
TCZ 10 mg/kg ($n=30$)	–0.07 (0.11)	–0.09 (0.12)	–0.11 (0.12)	–0.13 (0.14)	–0.08 (0.13)	–0.09 (0.17)	–0.02 (0.15)	–0.02 (0.14)	0.02 (0.16)	–0.01 (0.14)
TCZ 20 mg/kg ($n=31$)	–0.08 (0.08)	–0.11 (0.11)	–0.11 (0.14)	–0.10 (0.15)	–0.05 (0.19)	–0.11 (0.19)	–0.03 (0.21)	–0.01 (0.22)	0.02 (0.22)	0.04 (0.14)
LDL										
PBO ($n=29$)	–0.11 (0.43)	–0.11 (0.43)	0.05 (0.53)	0.00 (0.50)	0.04 (0.56)	–0.18 (0.47)	0.06 (0.59)	–0.11 (0.49)	–0.09 (0.47)	–0.15 (0.51)
TCZ 10 mg/kg ($n=30$)	–0.13 (0.21)	–0.03 (0.32)	0.08 (0.33)	0.13 (0.35)	0.33 (0.38)	0.22 (0.37)	0.12 (0.40)	–0.03 (0.46)	0.08 (0.44)	–0.09 (0.40)
TCZ 20 mg/kg ($n=31$)	–0.15 (0.24)	–0.02 (0.30)	0.10 (0.37)	0.16 (0.42)	0.39 (0.40)	0.23 (0.42)	0.35 (0.50)	0.09 (0.55)	0.23 (0.45)	0.14 (0.42)

[a]Number reflects those subjects who received a study treatment dose. Mean (S.D.).

average therapeutic TCZ exposure (AUC, C_{max}) at steady-state of an 8 mg/kg dose given every 4 weeks to an RA patient. Serum levels of total cholesterol (TCh), high-density lipoprotein-cholesterol (HDL) and low-density lipoprotein-cholesterol (LDL) were assessed after a 12-hour fast at baseline (BL), days 1, 2, 3, 4, 5, 8, 11, 15, 22, 29, and follow-up (Day 50 ± 2).

Results: Administration of a single dose of TCZ resulted in a transient small increase in TCh and LDL, tending to peak around Day 8 for both TCZ groups. The magnitude of these increases in healthy subjects were markedly less than those reported for RA patients treated with TCZ and by Day 50, levels of TCh, HDL, LDL in the 10 mg/kg group had returned to, or were lower than, baseline levels (Table 1). Mean values for TCh, HDL, and LDL were within the normal range for all groups.

Conclusion: There were no meaningful increases in TCh, HDL or LDL in healthy subjects with either a single therapeutic or supra-therapeutic dose of TCZ. This observation is supportive of the notion that the reported elevation of cholesterol levels with TCZ in RA patients is a consequence of suppression of the inflammatory burden and the return of cholesterol levels towards a non-inflammatory state, as found in the general population.

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