

SAFETY OF TOCILIZUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS: AN INTERIM ANALYSIS UP TO 3.5 YEARS OF TREATMENT IN LONG-TERM EXTENSION STUDIES

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The safety of tocilizumab (TCZ) as monotherapy or with DMARDs has been shown in patients (pts) with rheumatoid arthritis (RA) in phase 3 clinical trials and long-term extension studies. The objective of this analysis was to assess the longer-term safety of TCZ using pooled data from ongoing extension studies.

Methodology: The analysis included all pts who received ≥ 1 dose of TCZ in phase 3 trials (OPTION, TOWARD, RADIATE, AMBITION, LITHE), in a phase 1 study, or in ongoing, open-label extension studies. Safety data were pooled and analyzed from the time of initial TCZ exposure through Feb. 6, 2009.

Results: TCZ was administered to 4009 pts, mean treatment duration was 2.4 yrs, and total follow-up was 9414 pt-yrs (PY). Overall withdrawal rate due to adverse events (AEs) was 5.8/100 PY. The most common AEs that led to withdrawal were investigations (1.3/100 PY, primarily of liver transaminase elevations), infections/infestations (1.1/100 PY), and neoplasms (benign, malignant, unspecified; 0.7/100 PY). Overall serious AE rate was 14.9/100 PY, with a serious infection rate of 4.7/100 PY. Overall death rate was 0.53/100 PY, with a death rate from infection of 0.13/100 PY. Rate of GI perforations (mostly complicated diverticulitis) was 2.8/1000 PY. Malignancies occurred at a rate of 1.19/100 PY, with no evidence of a higher occurrence of any specific type. Rates/100 PY of myocardial infarction and stroke were 0.25 and 0.19, respectively, and did not increase with continued TCZ exposure. Mean total cholesterol, LDL, HDL, and triglyceride levels increased by wk 6 and remained relatively stable over time. The increase in LDL during treatment returned to baseline levels in pts who received lipid-lowering agents. Proportions of pts with liver transaminase elevations $>3\times$ ULN were 9.5% for ALT and 3.1% for AST. These elevations were not associated with clinical hepatitis or hepatic dysfunction.

Conclusion: The safety profile of TCZ has been well characterized in the largest development program for a biologic agent used in RA. No new safety signals have emerged with prolonged exposure to TCZ in the long-term extension program. Along with long-term efficacy results these data support a favorable risk/benefit ratio for TCZ in pts with moderate to severe RA.