

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Early effects of first-line treatment with anti-interleukin-6 receptor antibody tocilizumab for chronic active antibody-mediated rejection in kidney transplantation

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1741500> since 2022-03-08T16:12:03Z

Published version:

DOI:10.1111/ctr.13908

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

- antibodies detected pretransplant on kidney graft outcomes is both proper and synergistic with donor-specific anti-HLA antibodies. *Nephrology*. 2019;24(3):347-356. doi:10.1111/nep.13239
43. Reinsmoen NL, Lai CH, Heidecke H, et al. Anti-angiotensin type 1 receptor antibodies associated with antibody mediated rejection in donor HLA antibody negative patients. *Transplantation*. 2010;90(12):1473-1477. doi:10.1097/TP.0b013e3181fd97f1
44. Philogene MC, Bagnasco S, Kraus ES, et al. Anti-angiotensin II type 1 receptor and anti-endothelial cell antibodies: A cross-sectional analysis of pathological findings in allograft biopsies. *Transplantation*. 2017;101(3):608-615. doi:10.1097/TP.0000000000001231
45. Tackey E, Lipsky PE, Illei GG. Rationale for interleukin-6 blockade in systemic lupus erythematosus. *Lupus*. 2004;13(5):339-343. doi:10.1191/0961203304lu1023oa
46. Chafin CB, Regna NL, Dai R, Caudell DL, Reilly CM. MicroRNA-let-7a expression is increased in the mesangial cells of NZB/W mice and increases IL-6 production in vitro. *Autoimmunity*. 2013;46(6):351-362. doi:10.3109/08916934.2013.773976
47. Jordan SC, Choi J, Kim I, et al. Interleukin-6, A cytokine critical to mediation of inflammation, autoimmunity and allograft rejection: Therapeutic implications of IL-6 receptor blockade. *Transplantation*. 2017;101(1):32-44. doi:10.1097/TP.0000000000001452
48. Itoh M, Nakadate K, Horibata Y, et al. The structural and functional organization of the podocyte filtration slits is regulated by Tjp1/ZO-1. *PLoS One*. 2014;9(9):1-11. doi:10.1371/journal.pone.0106621
49. Azzarello JT, Lin HK, Gherezghiher A, et al. Expression of AKR1C3 in renal cell carcinoma, papillary urothelial carcinoma, and Wilms' tumor. *Int J Clin Exp Pathol*. 2010;3(2):147-155.
50. Maggiorani D, Dissard R, Belloy M, et al. Shear stress-induced alteration of epithelial organization in human renal tubular cells. *PLoS One*. 2015;10(7):1-21. doi:10.1371/journal.pone.0131416
51. Sun CJ, Jin Y, Zhang WY, Li L, Liu XW. Role of AKR1C3 in renal injury and glibenclamide is anti-inflammatory in preeclamptic rats. *Gene*. 2018;662(October 2017):1-9. doi:10.1016/j.gene.2018.04.004

ACKNOWLEDGMENTS

A.L., R.P., A.M., I.A. and L.B. wrote the main manuscript text; C.G. and G.C. performed gene expression analysis; A.M. performed immunofluorescence analysis; C.C. performed antibody tests; A.B. revised histological data; F.F. performed statistical analysis; A.L., R.P., C.G., A.M., E.G., G.C., I.A., A.B., C.C., F.F., M.M., M.R. and L.B. contributed to the conception, design and analysis of the data; A.L., R.P., C.G., A.M., E.G., G.C., I.A., A.B., C.C., F.F., M.M., M.R. and L.B. contributed to the revision and approval of the final manuscript. The authors thank Drs. M. Scaldaferrri and F. Cattel (Pharmaceutical Committee, Città della Salute e della Scienza di Torino, University Hospital) for their expert support.

This work was funded by a CAMGAUTO14 grant from the University of Turin - Department of Medical Sciences to L.B.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Table 1. Baseline characteristics of the studied population

	TCZ-treated patients (n=15)
Recipient characteristics	
Age at transplant (yrs), median (IQR)	38.3 (23.0-47.5)
Gender male, No. (%)	12 (80.0)
Previous kidney transplantation, No. (%)	2 (13.3)
Time between dialysis and transplant (yrs), median (IQR)	2.4 (1.1-3.0)
Donor characteristics	
Age (yrs), median (IQR)	45.0 (32.5-52.5)
Deceased donor, No. (%)	13 (86.7)
ABO-incompatible donor, No. (%)	1 (6.7)
Cold ischemia time (h), median (IQR)	15.3 (13.6-17.8)
Extended-criteria donors, No. (%)	3 (20.0)
Delayed Graft Function ¹ , No. (%)	2 (13.3)
Immunology at the time of transplantation	
HLA mismatches, median (IQR)	4 (3-4.5)
Anti-HLA DSA positive, No. (%)	1 (6.7)
vPRA (%), median (IQR)	3.5 (0-83.8)
Functional data at discharge	
sCr (mg/dL), median (IQR)	1.65 (1.50-1.94)
eGFR (mL/min/1,73 m ²), median (IQR)	45.1 (39.1-54.7)
Proteinuria (g/day), median (IQR)	0.58 (0.37-0.80)
Time from transplantation to treatment (yrs), median (IQR)	7.1 (4.9-14.4)
Immunology at the time of cAMR	
Anti-HLA DSA positive, No. (%)	15 (100)
Class I, No.	1
Class II, No.	14
Anti-angiotensin type 1 receptor antibody positive, No. (%)	11 ² (84.6)
Functional data at the time of cAMR	
sCr (mg/dL), median (IQR)	1.60 (1.50-1.78)
eGFR (mL/min/1,73 m ²), median (IQR)	54.5 (47.5-56.8)

Proteinuria (g/day), median (IQR)	1.10 (0.60-1.52)
Rejection episodes before cAMR, No.	1 ³
Histological findings at the time of cAMR	
Chronic glomerulopathy (cg), median (IQR)	3 (2-3)
Microvascular inflammation (g + ptc), median (IQR)	3 (2-4)
Follow-up (months), median (IQR)	20.7 (18.0-27.8)

vPRA: virtual panel reactive antibody; sCr: serum creatinine; eGFR: estimated glomerular filtration rate; AMR: antibody-mediated rejection; TCMR: T-cell-mediated rejection; SD: standard deviation

¹ Intended as use of dialysis in the first week after kidney transplantation.

² Tested in 13/15 patients with available sera

³ Acute AMR 30 months before cAMR diagnosis

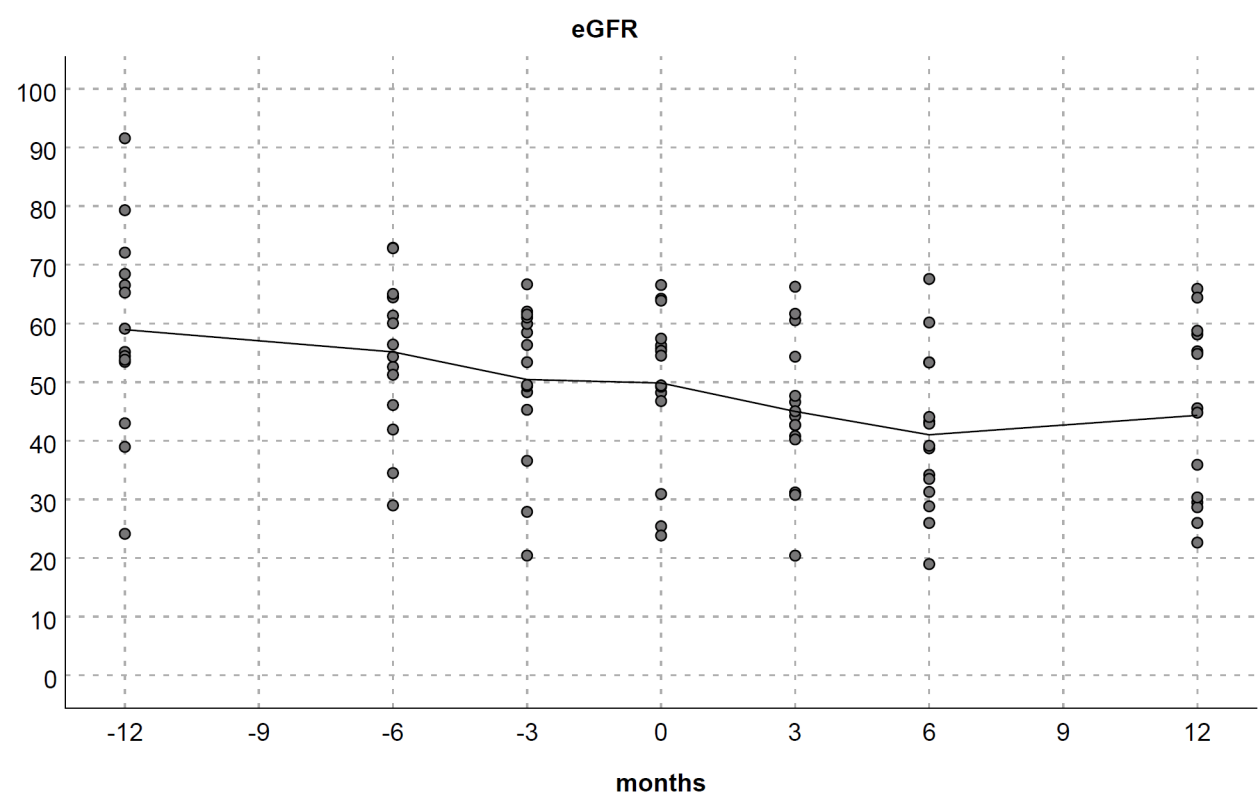
Table 2. Analysis of histological and serological changes pre- and post-tocilizumab treatment

	Pre TCZ	Post TCZ	p
glomerulitis (g), median (IQR)	2 (0-2)	1 (0-1)	0.015
peritubular capillaritis (ptc), median (IQR)	2 (1-2)	1 (0-2)	0.144
microvascular inflammation (g + ptc), median (IQR)	3 (2-4)	2 (1-2.5)	0.145
C4d score, median (IQR)	1 (0-2)	1 (0-2.5)	0.608
chronic glomerulopathy (cg), median (IQR)	3 (2-3)	3 (3-3)	0.206
interstitial fibrosis (ci), median (IQR)	1 (1-2)	1 (1-2)	0.655
tubular atrophy (ct), median (IQR)	1 (1-2)	1 (1-2)	0.414
ci + ct score, median (IQR)	2 (2-3.5)	3 (2-4)	0.448
inflammation in area of IFTA (i-IFTA), median (IQR)	1 (1-1)	1 (1-2)	0.180
arteriolar hyalinosis (ah), median (IQR)	2 (1-2)	2 (1-2)	0.257
vascular fibrointimal thickening (cv), median (IQR)	1 (0-1)	1 (1-1)	0.405
HLA-iDSA, MFI, median (IQR)	22600 (21700-23700)	18200 (12650-22150)	0.002
AT1R-Ab, level (U/mL), median (IQR)	15.8 (12.5-16.6)	8.4 (6.8-11.3)	0.003

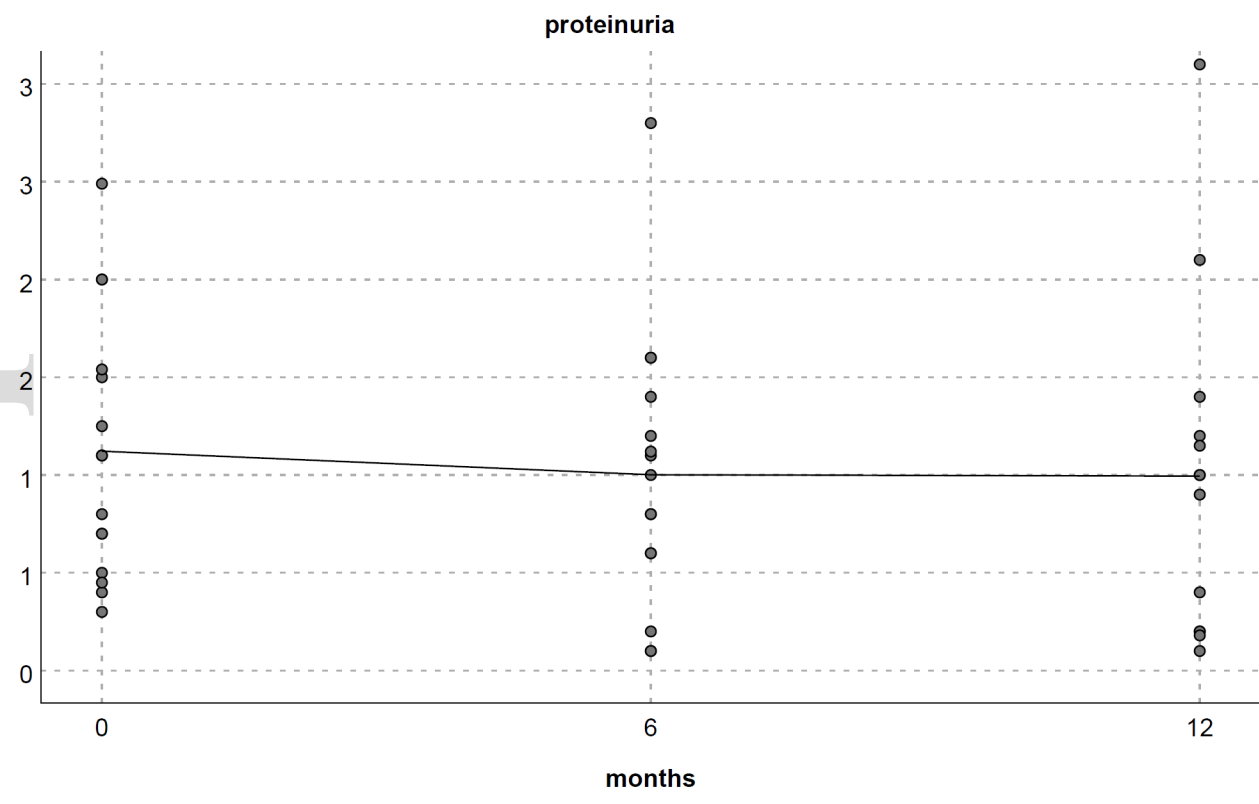
TCZ: tocilizumab; IFTA: interstitial fibrosis and tubular atrophy; iDSA: immunodominant DSA;

AT1R-Ab: Angiotensin II receptor type 1 antibody

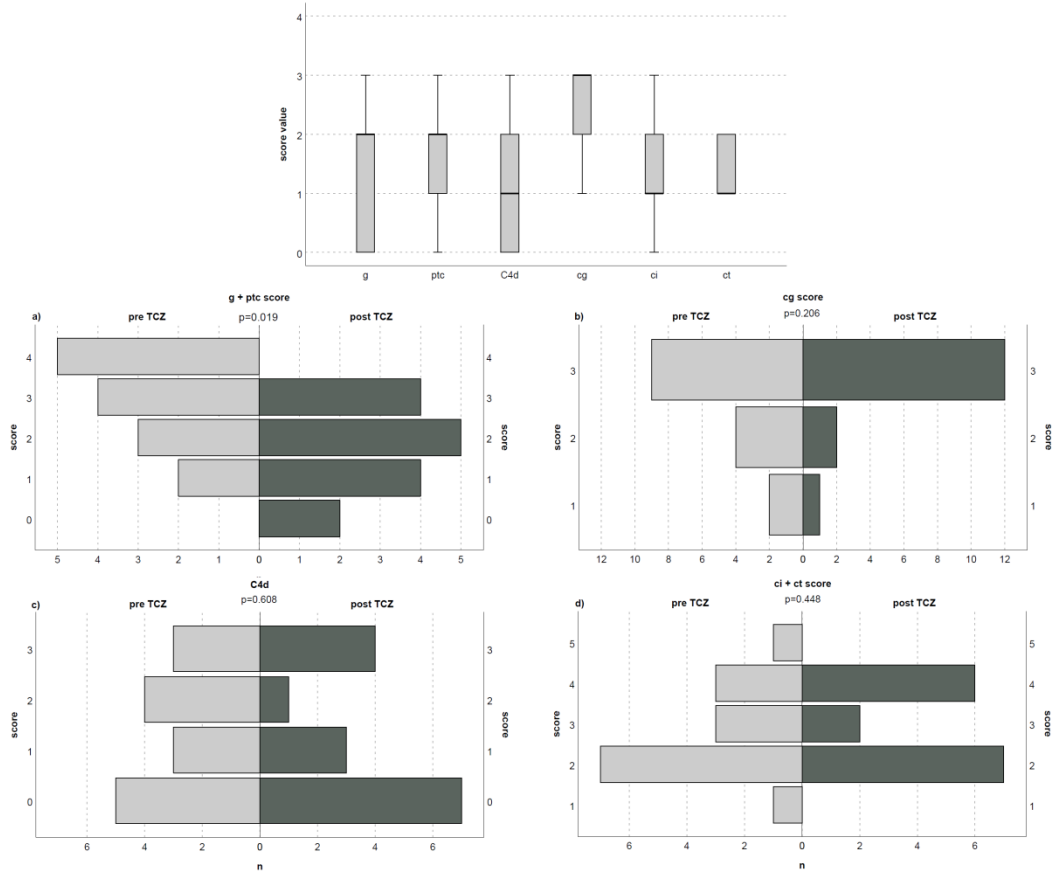
A



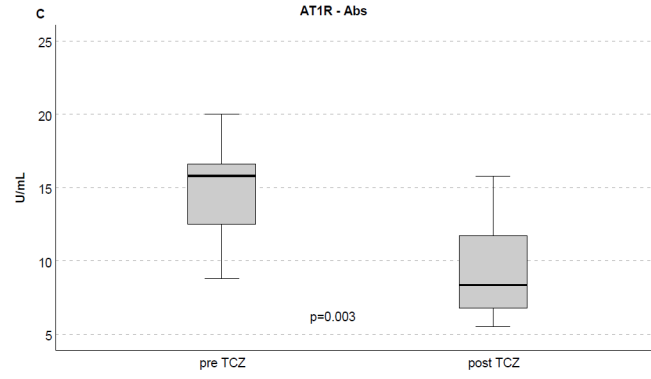
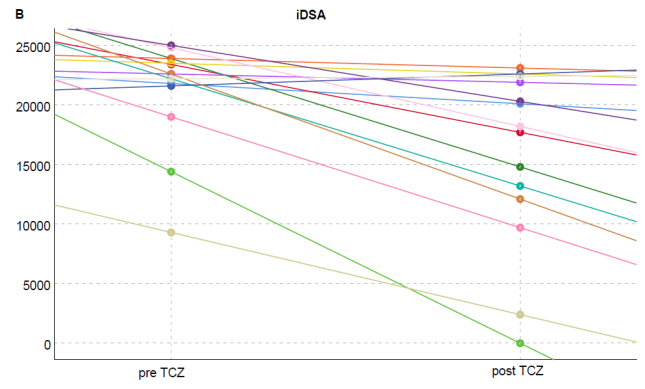
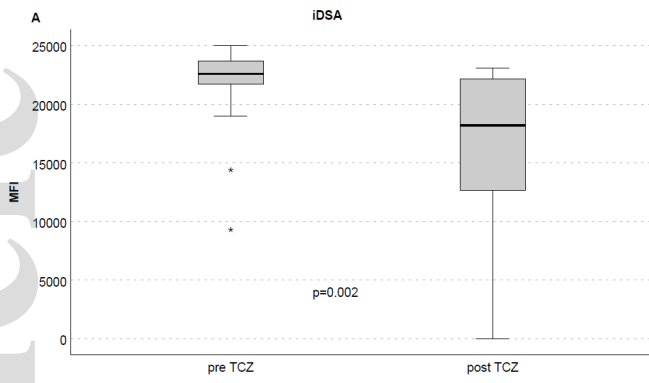
B



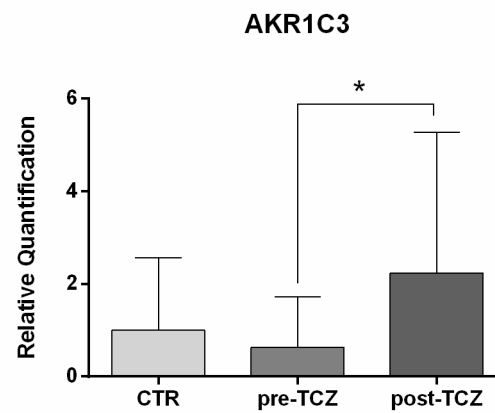
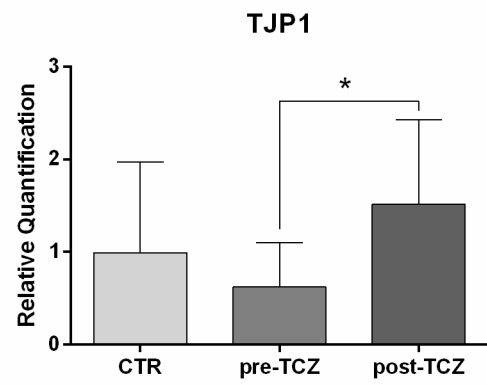
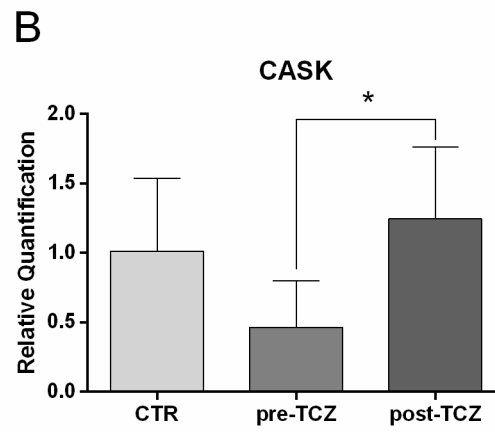
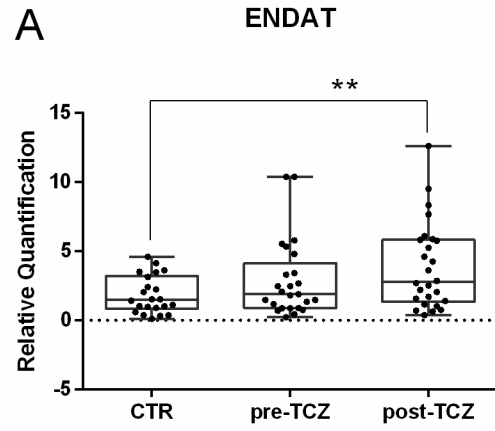
ctr_13908_f1.tif

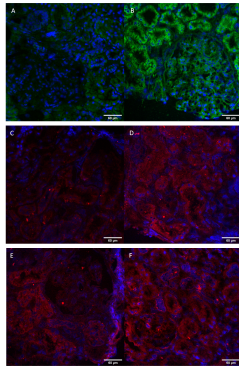


ctr_13908_f2.tif



ctr_13908_f3.tif





ctr_13908_f5.tiff