**SUPPLEMENTARY MATERIAL**

**Table S1.** Summary of Lipid Changes With Tocilizumab in Clinical Trials of RA

| Clinical Study, Publication Year (reference) | Study Population | Primary Outcome | Findings in Patients Treated With TCZ |
|---|---|---|---|
| CHARISMA, 2006 [21] | MTX-IR<br>TCZ 2 mg/kg (*n* = 53)<br>TCZ 4 mg/kg (*n* = 54)<br>TCZ 8 mg/kg (*n* = 52)<br>TCZ 2 mg/kg + MTX (*n* = 52)<br>TCZ 4 mg/kg + MTX (*n* = 49)<br>TCZ 8 mg/kg + MTX (*n* = 50)<br>MTX (*n* = 49) | The proportion of patients who achieved an ACR20 response at week 16 | Moderate reversible ↑ in mean levels of fasting TC, HDL-C, and TGs in groups receiving TCZ; mean atherogenic index remained largely unchanged |
| SAMURAI, 2007 [22] | csDMARD-IR patients<br>TCZ 8 mg/kg (*n* = 803)<br>csDMARD (*n* = 413) | Mean change in total modified Sharp scores from baseline to week 52 | ↑ TC, TGs, LDL-C, and HDL-C levels were reported in 38%, 17%, 26%, and 24% of patients in the TCZ groups, respectively<br>No change in atherogenic index (TC/HDL-C); no CV complications observed in association with abnormal lipids |

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| OPTION, 2008 [13] | MTX-IR<br>TCZ 4 mg/g + MTX (*n* = 213)<br>TCZ 8 mg/kg + MTX (*n* = 205)<br>PBO + MTX (*n* = 204) | The proportion of patients who achieved an ACR20 response at week 24 | ↑ Mean plasma concentrations of TC, HDL-C, and LDL-C from baseline to week 6 in patients treated with TCZ, which remained elevated at weeks 14 and 24<br>Elevations in cholesterol coincided with moderate to large decreases in CRP |
| TOWARD, 2008 [15] | csDMARD-IR patients<br>TCZ 8 mg/kg + csDMARD (*n* = 803)<br>PBO + csDMARD (*n* = 413) | The proportion of patients who achieved an ACR20 response at week 24 | ↑ Proportion of patients shifted to higher elevations from BL for TC (<240 to ≥240 mg/dl), LDL-C (<160 to ≥160 mg/dl), and HDL-C (<60 to ≥60 mg/dl) vs PBO |
| AMBITION, 2010 [16] | MTX experienced<br>TCZ 8 mg/kg (*n* = 288)<br>MTX (*n* = 284) | The proportion of patients who achieved an ACR20 response at week 24 | ↑ Proportion of patients shifted to higher elevations from BL for TC (<200 to ≥240 mg/dl) and LDL-C (<100 to ≥160 mg/dl) vs MTX |
| LITHE, 2011 [17] | MTX experienced<br>TCZ 8 mg/kg + MTX (*n* = 399)<br>TCZ 4 mg/kg + MTX (*n* = 399)<br>PBO + MTX (*n* = 392) | Change from baseline in total Genant-modified Sharp score and physical function to week 52 | ↑ Proportion of patients shifted to higher elevations from BL for TC (<240 to ≥240 mg/dl), LDL-C (<160 to ≥160 mg/dl), and HDL-C (<60 to ≥60 mg/dl) vs MTX |
| REACTION, 2011 [23] | TCZ 8 mg/kg ± MTX at investigator's discretion (*n* = 229) | Change in DAS28-ESR from baseline to week 24 | TCZ + MTX (*n* = 86): |

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|---|---|---|---|
| | | | ↑ mean TC 17.7 mg/dl vs BL |
| | | | TCZ monotherapy (*n* = 80): |
| | | | ↑ mean TC 12.9 mg/dl vs BL |
| | | | ↑ Mean TC, TGs, HDL-C, and LDL-C were mild; changes clinically significant in 15 patients |
| TAMARA, 2011 [24] | TCZ 8 mg/kg (*n* = 286) | The proportion of patients who achieved low disease activity scores (DAS28 ≤3.2) at week 24 | TNFi pretreatment (*n* = 119) |
| | | | ↑ LDL-C in 30.3%; ↑ LDL-C >160 mg/dl in 24.4% |
| | | | csDMARD pretreatment (*n* = 163) |
| | | | ↑ LDL-C in 25.8%; ↑ LDL-C >160 mg/dl in 20.2% |
| ROSE, 2012 [25] | csDMARD-IR patients<br>TCZ 8 mg/kg + csDMARD (*n* = 412)<br>PBO + csDMARD (*n* = 207) | The proportion of patients who achieved an ACR50 response at week 24 | ↑ Mean TC, LDL-C, HDL-C, and TC vs PBO; most of the increase was within the first 4-8 weeks of therapy and plateaued by weeks 12-16 |
| ADACTA, 2013 [20] | MTX-IR patients<br>TCZ 8 mg/kg + PBO (*n* = 163) | Change in DAS28 from baseline to week 24 | ↑ Mean LDL-C vs ADA |

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|---|---|---|---|
| | ADA 40 mg + PBO (*n* = 162) | | |
| ACT-RAY, 2013 [26] | MTX-IR<br>TCZ + MTX (*n* = 277)<br>TCZ + PBO (*n* = 276) | DAS28-ESR remission rate at week 24 | ↑ Mean TC levels from 93.1 vs 92.7 mg/dl at baseline to 102.4 vs 103.5 mg/dl at week 24 in the TCZ + MTX vs TCZ + PBO groups |
| MEASURE, 2015 [27] | MTX-IR patients<br>TCZ 8 mg/kg + MTX (*n* = 69)<br>PBO + MTX (*n* = 63) | Change from baseline in pulse wave velocity (vascular function) and small LDL particle number at week 12 | ↑ TC, TGs, and LDL-C vs PBO<br>↓ HDL-SAA, sPLA2-IIA, lipoprotein(a), and fibrinogen vs PBO |

| **SC Studies, Year [reference]** | **Study Population** | **Primary Outcome** | **Findings** |
|---|---|---|---|
| SUMMACTA, 2014 [19] | csDMARD-IR patients<br>TCZ-SC + PBO-IV (*n* = 631)<br>TCZ-IV + PBO-SC (*n* = 631) | To demonstrate the noninferiority of TCZ-SC to TCZ-IV with regard to the proportion of patients in each group achieving an ACR20 response at week 24 using a 12% noninferiority margin | ↑ Proportion of patients in TCZ-SC group shifted to higher elevations from BL for TC vs TCZ-IV group (<200 to ≥200 mg/dl; largest categorical shift: <200 to ≥240 mg/dl)<br>Clinically relevant shifts in LDL-C, HDL-C, and TGs were similar between groups |
| SUMMACTA OLE, 2015 [28] | csDMARD-IR patients initially randomized to TCZ-SC or TCZ-IV were re-randomized to TCZ-SC or TCZ-IV[a]: | 72-week OLE to assess the maintenance of clinical responses and safety through week 97 | The proportion of patients reporting shifts in TC, LDL-C, HDL-C, and TGs after initiation of TCZ was higher in the TCZ-SC arm than in the TCZ-IV arm at |

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|---|---|---|---|
| | TCZ-SC (*n* = 521)<br>TCZ-SC → IV (*n* = 48)<br>TCZ-IV (*n* = 372)<br>TCZ-IV → SC (*n* = 186) | | week 97 (TC, 26.1% vs 21.0%; LDL-C, 27.7% vs 23.2%; HDL-C, 3.2% vs 3.9%; and TGs, 23.8% vs 17.5%) |
| BREVACTA, 2014 [18] | csDMARD-IR patients<br>TCZ-SC + csDMARDs (*n* = 437)<br>PBO-SC + csDMARDs (*n* = 219) | The proportion of patients who achieved an ACR20 response at week 24 | ↑ Proportion of patients shifted to higher elevations from BL for TC (<200 to ≥240 mg/dl), LDL-C (<100 to ≥160 mg/dl), and TGs (<150 to ≥150 mg/dl) vs PBO |
| BREVACTA OLE (Kivitz A, unpublished observations, 2015) | csDMARD-IR patients initially randomized to TCZ-SC or PBO received open-label TCZ-SC<br>Continued TCZ-SC (*n* = 338)<br>PBO → TCZ-SC (*n* = 119) | 72-week OLE to assess the maintenance of clinical responses and safety through week 96 | Patients who switched from placebo to TCZ-SC at week 24 experienced shifts in levels of lipid parameters similar to those in patients who were randomized to TCZ-SC in the initial 24-week period |
| MUSASHI, 2014 [29] | csDMARD-IR patients<br>TCZ-SC monotherapy (*n* = 173)<br>TCZ-IV monotherapy (*n* = 173) | To demonstrate the noninferiority of TCZ-SC monotherapy to TCZ-IV monotherapy with regard to the proportion of patients in each group achieving an ACR20 response at week 24 using an 18% noninferiority margin | Shift from baseline (TCZ-SC):<br>TC (<200 to ≥240 mg/dl), *n* = 32/136<br>HDL-C (<40 to ≥60 mg/dl), *n* = 0/29<br>LDL-C (<100 to ≥160 mg/dl), *n* = 1/93 |

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|---|---|---|---|
| | | | Shift from baseline, (TCZ-IV):<br>TC (<200 to ≥240 mg/dl), *n* = 35/130<br>HDL-C (<40 to ≥60 mg/dl), *n* = 0/14<br>LDL-C (<100 to ≥160 mg/dl), *n* = 4/73 |
| MUSASHI LTE, 2015 [30] | Patients previously received 24 weeks of double-blind treatment with either TCZ-SC monotherapy or TCZ-IV monotherapy<br>TCZ-SC monotherapy (*n* = 346) | 84-week OLE to assess the maintenance of clinical responses and safety through week 108 | Shift from baseline:<br>TC (<200 to ≥240 mg/dl), *n* = 32/266<br>HDL-C (<40 to ≥60 mg/dl), *n* = 5/43<br>LDL-C (<100 to ≥160 mg/dl), *n* = 4/166 |

*ACR20* 20% improvement in response per the American College of Rheumatology criteria, *ADA* adalimumab, *BL* baseline, *CRP* C-reactive protein, *csDMARD*, conventional synthetic disease-modifying antirheumatic drug, *CV* cardiovascular, *DAS28-ESR* disease activity score in 28 joints using the erythrocyte sedimentation rate, *HDL-C* high-density-lipoprotein cholesterol, *HDL-SAA* HDL-associated serum amyloid A, *IR* inadequate response, *IV* intravenous, *LDL-C* low-density-lipoprotein cholesterol, *LTE* long-term extension, *MTX* methotrexate, *OLE* open-label extension, *PBO* placebo, *SC* subcutaneous, *sPLA2-IIA* secreted phospholipase A2-IIA, *TC* total cholesterol, *TCZ* tocilizumab, *TG* triglyceride, *TNFi* tumor necrosis factor inhibitor.

[a] After a 24-week double-blind period, patients receiving TCZ-SC were re-randomized 11:1 to TCZ-SC or TCZ-IV (TCZ-SC → IV), and patients receiving TCZ-IV were re-randomized 2:1 to TCZ-IV or TCZ-SC (TCZ-IV → SC).

**Table S2.** Classification of Fasting Lipid Parameters and Cardiovascular Risk

| **National Cholesterol Education Program ATP III Classification** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **TC, mg/dl** | | **LDL-C, mg/dl** | | **HDL-C, mg/dl** | | **TGs, mg/dl** | |
| <200 | Desirable | <100 | Optimal | <40 | Low | <150 | Normal |
| 200-239 | Borderline high | 100-129 | Near optimal/ above optimal | 40-59 | Normal | 150-499 | High |
| ≥240 | High | 130-159 | Borderline high | ≥60 | High | ≥500 | Very high |
| — | — | 160-189 | High | — | — | — | — |
| — | — | ≥190 | Very high | — | — | — | — |

| **TC:HDL-C and Risk—Framingham Heart Study** | | | |
|---|---|---|---|
| **TC:HDL-C Ratio** | **Ideal** | **Moderate** | **High** |
| Men | <3.5 | 3.5-5.0 | >5.0 |
| Women | <3.0 | 3.0-4.4 | >4.4 |

*ATP* Adult Treatment Panel, *HDL-C* high-density-lipoprotein cholesterol, *LDL-C* low-density-lipoprotein cholesterol, *TC* total cholesterol, *TG* triglyceride.

**Table S3.** Description of Statin Use Over Time by TCZ Treatment Group (safety population)

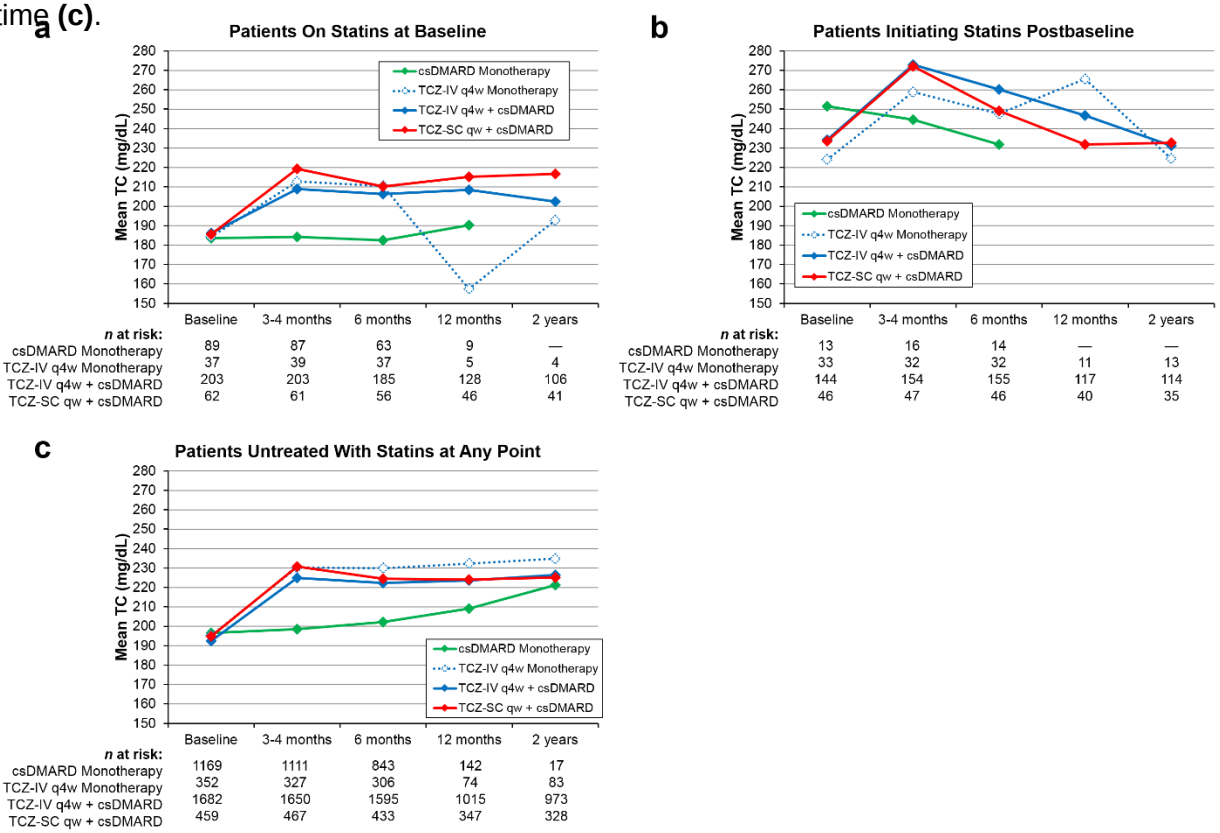
| **Statin Use, *n* (%)** | **csDMARD Monotherapy (*N* = 1361)** | **TCZ-IV 8 mg/kg q4w Monotherapy (*N* = 450)** | **TCZ-IV 8 mg/kg q4w + csDMARD (*N* = 2213)** | **TCZ-SC 162 mg qw + csDMARD (*N* = 631)** |
|---|---|---|---|---|
| Baseline, *n* | 1361 | 450 | 2213 | 631 |
| Simvastatin | 41 (3.0) | 17 (3.8) | 80 (3.6) | 29 (4.6) |
| Atorvastatin | 35 (2.6) | 12 (2.7) | 70 (3.2) | 20 (3.2) |
| Rosuvastatin | 6 (0.4) | 5 (1.1) | 21 (0.9) | 8 (1.3) |
| Pravastatin | 7 (0.5) | 5 (1.1) | 21 (0.9) | 6 (1.0) |
| Lovastatin | 3 (0.2) | 1 (0.2) | 13 (0.6) | 5 (0.8) |
| Ezetimibe/simvastatin | 3 (0.2) | 1 (0.2) | 16 (0.7) | 3 (0.5) |
| Other[a] | 4 (0.3) | 2 (0.4) | 10 (0.5) | 1 (0.2) |
| Total | 99 (7.3) | 42 (9.3) | 230 (10.4) | 72 (11.4) |
| Post-baseline 3-4 months, *n* | 1330 | 432 | 2184 | 614 |
| Simvastatin | 43 (3.2) | 24 (5.6) | 91 (4.2) | 41 (6.7) |
| Atorvastatin | 38 (2.9) | 14 (3.2) | 87 (4.0) | 22 (3.6) |
| Rosuvastatin | 7 (0.5) | 7 (1.6) | 27 (1.2) | 9 (1.5) |
| Pravastatin | 8 (0.6) | 6 (1.4) | 21 (1.0) | 6 (1.0) |
| Lovastatin | 3 (0.2) | 1 (0.2) | 15 (0.7) | 5 (0.8) |
| Ezetimibe/simvastatin | 3 (0.2) | 4 (0.9) | 20 (0.9) | 3 (0.5) |
| Other[a] | 5 (0.4) | 2 (0.5) | 10 (0.5) | 2 (0.3) |
| Total | 107 (8.0) | 54 (12.5) | 264 (12.0) | 88 (14.3) |
| Post-baseline 6 months, *n* | 980 | 415 | 2099 | 593 |
| Simvastatin | 35 (3.6) | 26 (6.3) | 88 (4.2) | 44 (7.4) |
| Atorvastatin | 24 (2.4) | 15 (3.6) | 82 (3.9) | 22 (3.7) |
| Rosuvastatin | 6 (0.6) | 8 (1.9) | 28 (1.3) | 10 (1.7) |
| Pravastatin | 9 (0.9) | 6 (1.4) | 19 (0.9) | 6 (1.0) |
| Lovastatin | 1 (0.1) | 1 (0.2) | 16 (0.8) | 4 (0.7) |
| Ezetimibe/simvastatin | 3 (0.3) | 4 (1.0) | 21 (1.0) | 3 (0.5) |
| Other[a] | 4 (0.4) | 2 (0.5) | 13 (0.6) | 2 (0.3) |
| Total | 82 (8.4) | 60 (14.5) | 262 (12.4) | 90 (15.2) |
| Post-baseline 12 months, *n* | 195 | 169 | 1745 | 510 |
| Simvastatin | 6 (3.1) | 4 (2.4) | 80 (4.6) | 39 (7.6) |
| Atorvastatin | 4 (2.1) | 2 (1.2) | 74 (4.2) | 23 (4.5) |
| Rosuvastatin | 1 (0.5) | 1 (0.6) | 24 (1.4) | 8 (1.6) |
| Pravastatin | 2 (1.0) | 2 (1.2) | 16 (0.9) | 8 (1.6) |
| Lovastatin | 0 | 1 (0.6) | 16 (0.9) | 3 (0.6) |
| Ezetimibe/simvastatin | 1 (0.5) | 2 (1.2) | 25 (1.4) | 2 (0.4) |

| | | | | |
|---|---|---|---|---|
| Other[a] | 1 (0.5) | 0 | 10 (0.6) | 2 (0.4) |
| Total | 15 (7.7) | 12 (7.1) | 239 (13.7) | 85 (16.7) |
| Post-baseline 2 years, | 22 | 145 | 1555 | 453 |
| *n* Simvastatin | 0 | 5 (3.4) | 97 (6.2) | 35 (7.7) |
| Atorvastatin | 1 (4.5) | 7 (4.8) | 75 (4.8) | 23 (5.1) |
| Rosuvastatin | 0 | 0 | 25 (1.6) | 6 (1.3) |
| Pravastatin | 0 | 3 (2.1) | 23 (1.5) | 10 (2.2) |
| Lovastatin | 0 | 1 (0.7) | 11 (0.7) | 4 (0.9) |
| Ezetimibe/simvastatin | 0 | 2 (1.4) | 18 (1.2) | 1 (0.2) |
| Other[a] | 0 | 2 (1.4) | 7 (0.5) | 0 |
| Total | 1 (4.5) | 20 (13.8) | 248 (15.9) | 79 (17.4) |

*csDMARD* conventional synthetic disease-modifying antirheumatic drug, *IV* intravenous, *qw* every week, *q4w* every 4 weeks, *SC* subcutaneous, *TCZ* tocilizumab.

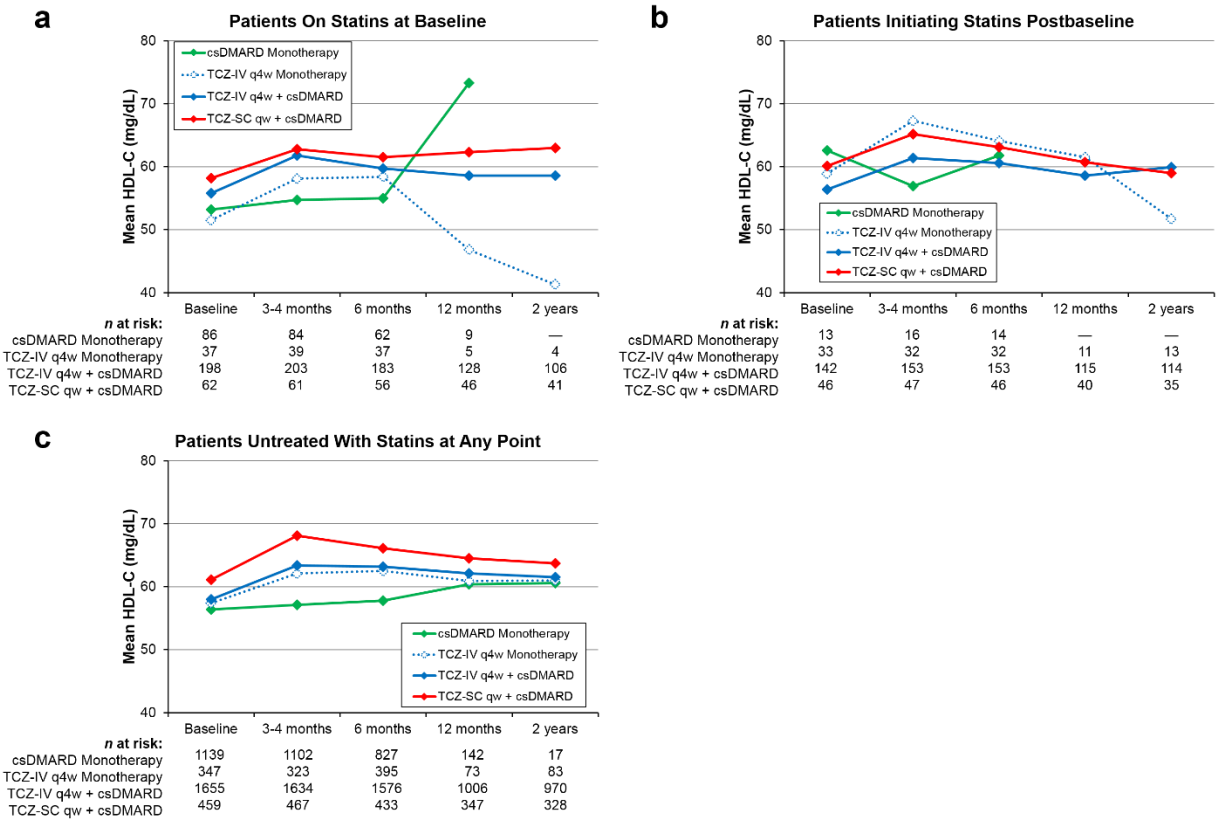
[a] Other lipid-lowering agents and statins used during the study include fluvastatin, amlodipine/atorvastatin, lovastatin/nicotinic acid, fluvastatin sodium, atorvastatin/ezetimibe, amlodipine besylate/atorvastatin calcium, and statin nitric oxide synthetase/unsaturated fatty acids.

**Fig. S1.** Mean TC levels over time in patients who were on statins at baseline **(a)**, patients who initiated statins post-baseline **(b)**, and patients who were untreated with statins at any time **(c)**.



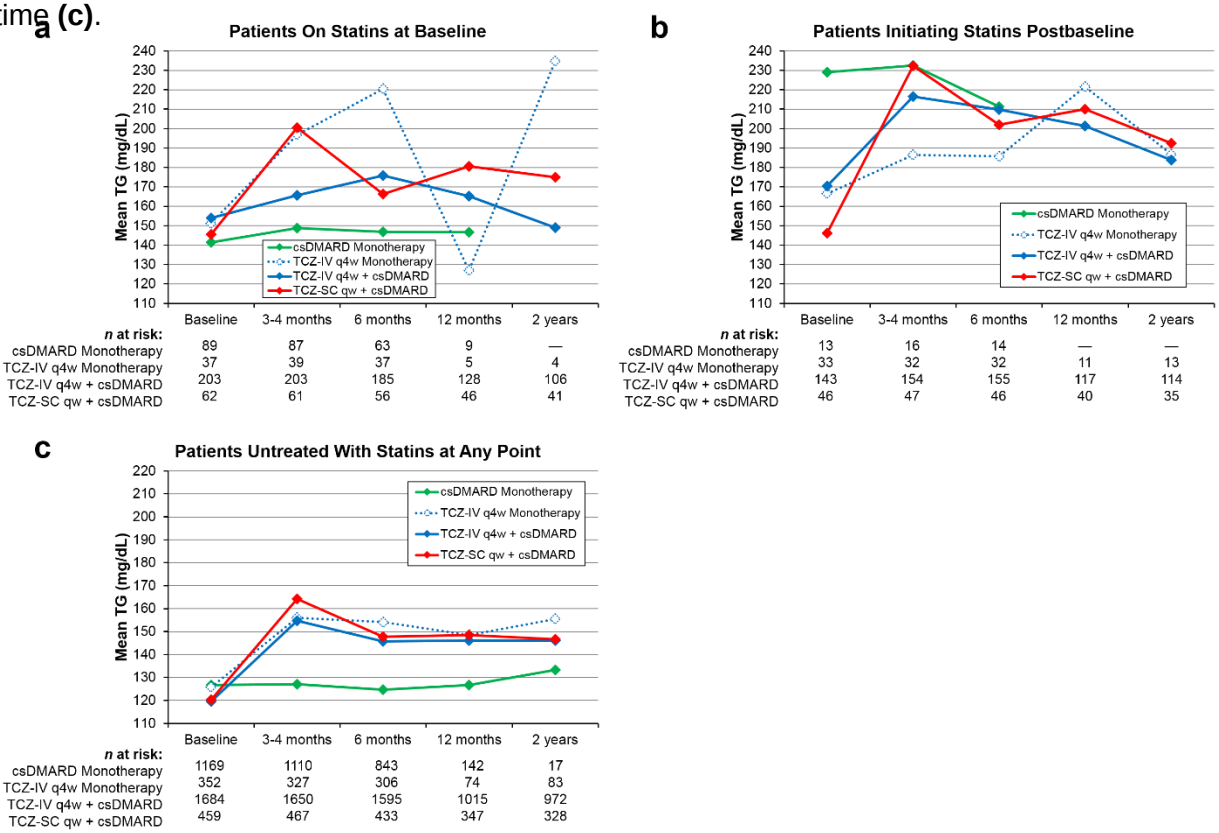

*csDMARD* conventional disease-modifying antirheumatic drug, *IV* intravenous, *qw* every week, *q4w* every 4 weeks, *SC* subcutaneous, *TC* total cholesterol, *TCZ* tocilizumab.

**Fig. S2.** Mean HDL-C levels over time in patients who were on statins at baseline **(a)**, patients who initiated statins post-baseline **(b)**, and patients who were untreated with statins at any time **(c)**.




*csDMARD* conventional synthetic disease-modifying antirheumatic drug, *HDL-C* high-density lipoprotein cholesterol, *IV* intravenous, *qw* every week, *q4w* every 4 weeks, *SC* subcutaneous, *TCZ* tocilizumab.

**Fig. S3.** Mean TG levels over time in patients who were on statins at baseline **(a)**, patients who initiated statins post-baseline **(b)**, and patients who were untreated with statins at any time **(c)**.




*csDMARD* conventional synthetic disease-modifying antirheumatic drug, *IV* intravenous, *qw* every week, *q4w* every 4 weeks, *SC* subcutaneous, *TG* triglyceride, *TCZ* tocilizumab.