**Supplemental Table 1. Selected characteristics of study patients in the 180 days before study entry: unmatched**.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Medicare**  **(N=19,883)** | | **IMS**  **(N=20,016)** | | **MarketScan**  **(N=22,664)** | |
|  | **TCZ**  **(N=6,265)** | **TNFi**  **(N=13,618)** | **TCZ**  **(N=4,738)** | **TNFi**  **(N=15,278)** | **TCZ**  **(N=5,716)** | **TNFi**  **(N=16,948)** |
| Mean ± standard deviation or percentage | | | | | | |
| **Demographics** |  |  |  |  |  |  |
| Age, years | 72.2 ± 6.0 | 72.1 ± 6.3 | 50.8 ± 11.7 | 50.0 ± 11.7 | 53.5 ± 12.6 | 51.9 ± 12.7 |
| Male | 16.9 | 17.1 | 18.2 | 21.9 | 16.8 | 21.1 |
| **Comorbidities** |  |  |  |  |  |  |
| Atrial fibrillation | 8.9 | 7.6 | 1.6 | 1.2 | 2.3 | 1.6 |
| CAD | 15.7 | 15.0 | 4.3 | 3.4 | 4.6 | 4.0 |
| Heart failure | 8.4 | 7.4 | 1.6 | 1.0 | 2.1 | 1.1 |
| Stroke/TIA | 3.8 | 3.2 | 0.9 | 0.9 | 1.3 | 1.0 |
| PVD | 7.6 | 8.7 | 1.3 | 1.1 | 1.7 | 1.3 |
| Hypertension | 80.6 | 79.9 | 46.0 | 42.8 | 49.7 | 46.2 |
| Diabetes | 26.0 | 28.2 | 13.2 | 12.7 | 15.4 | 13.7 |
| Hyperlipidemia | 55.5 | 52.5 | 27.0 | 22.7 | 26.3 | 22.3 |
| CKD | 5.0 | 5.1 | 3.7 | 3.6 | 3.3 | 3.4 |
| Comorbidity Index | 0.9 ± 1.8 | 0.8 ± 1.7 | 0.5 ± 1.3 | 0.4 ± 1.2 | 0.3 ± 1.1 | 0.2 ± 1.0 |
| CIRAS | 5.9 ± 1.2 | 5.8 ± 1.3 | 6.6 ± 1.7 | 6.6 ± 1.7 | 6.5 ± 1.8 | 6.5 ± 1.9 |
| **RA-related Treatment** | | |  |  |  |  |
| No. of prior DMARDs | |  |  |  |  |  |
| 1 | 6.2 | 10.3 | 6.6 | 11.7 | 11.8 | 11.3 |
| 2 | 27.5 | 38.0 | 22.6 | 37.4 | 20.9 | 36.9 |
| 3+ | 66.4 | 51.8 | 70.7 | 50.9 | 67.3 | 51.8 |
| Methotrexate | 70.3 | 69.5 | 71.2 | 71.3 | 68.6 | 72.1 |
| Hydroxychloroquine | 28.6 | 27.7 | 33.3 | 33.3 | 30.4 | 32.1 |
| Steroids | 80.1 | 73.3 | 77.4 | 73.9 | 72.0 | 71.7 |
| Recent steroid use | 71.0 | 63.8 | 68.0 | 63.5 | 63.3 | 61.5 |
| NSAID/COXIB | 26.3 | 27.1 | 34.1 | 35.9 | 30.4 | 34.1 |
| Opioids | 64.5 | 59.5 | 57.7 | 53.9 | 55.8 | 53.5 |
| **Other Medications** | | |  |  |  |  |
| No. of prescription drugs | 11.0 ± 5.3 | 11.6 ± 5.6 | 10.0 ± 6.1 | 10.4 ± 5.8 | 9.7 ± 6.4 | 10.4 ± 5.7 |
| Antibiotics | 57.9 | 54.2 | 47.9 | 47.9 | 46.5 | 48.2 |
| Antivirals | 4.8 | 4.4 | 6.3 | 5.5 | 5.4 | 5.4 |
| Lipid lowering drugs | 44.2 | 44.7 | 20.6 | 19.4 | 22.6 | 22.3 |
| Non-insulin antidiabetics | 14.3 | 15.5 | 7.3 | 7.4 | 7.9 | 8.0 |
| Insulin | 5.6 | 6.4 | 3.8 | 3.4 | 3.9 | 3.7 |
| Antidepressants | 38.2 | 36.7 | 37.3 | 34.9 | 35.6 | 34.7 |
| **Vaccines** |  |  |  |  |  |  |
| Flu vaccine | 37.1 | 33.9 | 18.9 | 16.9 | 17.3 | 15.9 |
| Pneumonia vaccine | 9.0 | 8.7 | 4.4 | 5.5 | 4.3 | 4.8 |
| Herpes zoster vaccine | 2.5 | 2.3 | 1.8 | 1.7 | 1.1 | 1.1 |
| **Health Care Utilization** | | | | | | |
| No. of CRP test ordered | 1.8 ± 1.8 | 1.4 ± 1.5 | 1.7 ± 1.7 | 1.3 ± 1.4 | 1.5 ± 1.7 | 1.2 ± 1.3 |
| Hospitalization | 11.3 | 10.6 | 6.5 | 6.6 | 6.7 | 6.3 |
| No. of PCP visits | 2.4 ± 2.7 | 2.4 ± 2.7 | 3.0 ± 7.3 | 2.7 ± 7.5 | 3.4 ± 9.8 | 2.9 ± 7.3 |

TCZ=tocilizumab, TNFi=tumor necrosis factor inhibitor, CAD=coronary artery disease, TIA=transient ischemic attack, PVD=peripheral vascular disease, CKD= chronic kidney disease, CIRAS=claims-based index for RA severity, DMARD=disease modifying antirheumatic drug, NSAID=nonsteroidal anti-inflammatory drug, COXIB=cyclooxygenase-2 inhibitor, PCP=primary care physician, ED=emergency department

**Supplemental Table 2. Selected characteristics of the secondary cohort in the 180 days before study entry: PS-matched with a 1:1 fixed ratio.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Medicare**  **(N=7,700)** | | **IMS**  **(N=6,016)** | | **MarketScan**  **(N=7,112)** | |
|  | **TCZ**  **(N=3,850)** | **Abatacept**  **(N=3,850)** | **TCZ**  **(N=3,008)** | **Abatacept**  **(N=3,008)** | **TCZ**  **(N=3,556)** | **Abatacept**  **(N=3,556)** |
| Mean ± standard deviation or percentage | | | | | | |
| **Demographics** |  |  |  |  |  |  |
| Age, years | 72.1 ± 6.0 | 72.0 ± 5.7 | 50.7 ± 11.7 | 50.8 ± 11.4 | 53.3 ± 12.6 | 53.5 ± 12.4 |
| Male | 17.8 | 17.5 | 18.2 | 18.6 | 18.2 | 18.4 |
| **Comorbidities** |  |  |  |  |  |  |
| Atrial fibrillation | 9.0 | 8.8 | 1.8 | 2.0 | 2.2 | 2.1 |
| CAD | 15.8 | 15.9 | 4.0 | 3.7 | 4.3 | 4.5 |
| Heart failure | 8.4 | 7.8 | 1.6 | 1.3 | 2.1 | 2.2 |
| Stroke/TIA | 4.0 | 3.9 | 1.0 | 0.9 | 1.3 | 1.2 |
| PVD | 7.8 | 7.6 | 1.3 | 1.2 | 1.8 | 1.8 |
| Hypertension | 80.3 | 80.1 | 44.7 | 45.7 | 49.2 | 49.8 |
| Diabetes | 26.2 | 26.3 | 12.7 | 12.2 | 15.3 | 15.3 |
| Hyperlipidemia | 55.6 | 56.1 | 26.3 | 26.1 | 26.0 | 26.2 |
| CKD | 5.4 | 5.5 | 4.0 | 4.1 | 3.4 | 3.4 |
| Comorbidity Index | 0.9 ± 1.8 | 0.9 ± 1.8 | 0.4 ± 1.2 | 0.4 ± 1.2 | 0.3 ± 1.1 | 0.3 ± 1.1 |
| CIRAS | 5.9 ± 1.3 | 5.9 ± 1.3 | 6.6 ± 1.7 | 6.7 ± 1.7 | 6.5 ± 1.9 | 6.5 ± 1.9 |
| **RA-related Treatment** | | |  |  |  |  |
| No. of prior DMARDs | |  |  |  |  |  |
| 1 | 5.2 | 4.9 | 7.0 | 6.6 | 10.9 | 11.0 |
| 2 | 29.2 | 29.1 | 24.7 | 25.1 | 22.3 | 22.3 |
| 3+ | 65.6 | 66.1 | 68.4 | 68.3 | 66.8 | 66.6 |
| Methotrexate | 71.3 | 72.2 | 72.8 | 72.5 | 71.6 | 71.5 |
| Hydroxychloroquine | 28.4 | 28.4 | 32.3 | 32.9 | 30.5 | 31.1 |
| Steroids | 79.8 | 79.8 | 77.9 | 77.3 | 74.3 | 74.4 |
| Recent steroid use | 71.3 | 71.3 | 68.6 | 67.3 | 65.4 | 65.4 |
| NSAID/COXIB | 26.6 | 26.2 | 33.6 | 32.4 | 31.1 | 31.4 |
| Opioids | 64.8 | 65.4 | 58.0 | 57.7 | 56.8 | 57.0 |
| **Other Medications** | | |  |  |  |  |
| No. of prescription drugs | 11.3 ± 5.4 | 11.4 ± 5.3 | 10.0 ± 6.1 | 9.9 ± 5.5 | 10.0 ± 6.3 | 10.0 ± 5.8 |
| Antibiotics | 57.9 | 56.7 | 47.8 | 48.2 | 47.6 | 48.0 |
| Antivirals | 4.7 | 4.7 | 6.5 | 6.2 | 5.3 | 5.3 |
| Lipid lowering drugs | 44.3 | 44.8 | 20.0 | 19.5 | 22.9 | 23.2 |
| Non-insulin antidiabetics | 14.8 | 15.4 | 6.8 | 6.7 | 8.2 | 8.5 |
| Insulin | 5.7 | 5.6 | 3.6 | 3.2 | 3.8 | 3.5 |
| Antidepressants | 38.2 | 38.8 | 36.1 | 35.1 | 35.5 | 35.5 |
| **Vaccines** |  |  |  |  |  |  |
| Flu vaccine | 36.2 | 36.3 | 18.4 | 18.5 | 16.8 | 16.9 |
| Pneumonia vaccine | 9.0 | 8.8 | 4.5 | 4.7 | 4.4 | 4.7 |
| Herpes zoster vaccine | 2.4 | 2.5 | 2.0 | 2.2 | 1.1 | 1.3 |
| **Health Care Utilization** | | | | | | |
| No. of CRP test ordered | 1.8 ± 1.7 | 1.7 ± 1.7 | 1.6 ± 1.5 | 1.6 ± 1.6 | 1.5 ± 1.6 | 1.4 ± 1.6 |
| Hospitalization | 12.4 | 12.4 | 7.1 | 7.4 | 7.0 | 6.5 |
| No. of PCP visits | 2.4 ± 2.7 | 2.5 ± 2.7 | 3.0 ± 7.8 | 3.0 ± 8.4 | 3.2 ± 8.9 | 3.2 ± 7.3 |

TCZ=tocilizumab, TNFi=tumor necrosis factor inhibitor, CAD=coronary artery disease, TIA=transient ischemic attack, PVD=peripheral vascular disease, CKD= chronic kidney disease, CIRAS=claims-based index for RA severity, DMARD=disease modifying antirheumatic drug, NSAID=nonsteroidal anti-inflammatory drug, COXIB=cyclooxygenase-2 inhibitor, PCP=primary care physician, ED=emergency department

**Supplemental Table 3. Combined secondary outcomes: 1:1 fixed ratio propensity score-matched as-treated analyses.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Tocilizumab (N=10,414)** | | | **Abatacept (N=10,414)** | | |  |  |
|  | Events | Person-years | IR a  (95%CI) | Events | Person-years | IR a  (95%CI) | HR  (95%CI) | Rate difference b |
| Serious bacterial infection | 331 | 8,619 | 3.84  (3.43, 4.25) | 234 | 9,121 | 2.57  (2.24, 2.89) | 1.50  (1.27, 1.78) | 1.27  (0.74, 1.80) |
| Herpes zoster | 13 | 8,743 | 0.15  (0.07, 0.23) | NR | 9,199 | 0.09  (0.03, 0.15) | 1.77  (0.73, 4.28) | - |
| Opportunistic infection | 14 | 8,745 | 0.16  (0.08, 0.24) | NR | 9,202 | 0.07  (0.01, 0.12) | 2.42  (0.92, 6.39) | - |
| Pyelonephritis/UTI | 38 | 8,728 | 0.44  (0.30, 0.57) | 47 | 9,181 | 0.51  (0.37, 0.66) | 0.85  (0.56, 1.32) | -0.07  (-0.27, 0.13) |
| Skin and soft tissue infection | 21 | 8,745 | 0.24  (0.14, 0.34) | NR | 9,200 | 0.05  (0.01, 0.10) | 2.82  (1.00, 7.95) | - |
| Diverticulitis | 49 | 8,734 | 0.56  (0.40, 0.72) | 29 | 9,188 | 0.32  (0.20, 0.43) | 1.79  (1.12, 2.84) | 0.24  (0.05, 0.43) |
| Pneumonia/upper respiratory tract infection | 119 | 8,696 | 1.37  (1.12, 1.61) | 92 | 9,167 | 1.00  (0.80, 1.21) | 1.37  (1.04, 1.80) | 0.37  (0.05, 0.69) |
| Septicemia/bacteremia | 145 | 8,694 | 1.67  (1.40, 1.94) | 442 | 29,320 | 1.51  (1.37, 1.65) | 1.04  (0.88, 1.22) | 0.16  (-0.15, 0.47) |

TCZ=tocilizumab, HR=hazard ratio, CI=confidence interval, UTI=urinary tract infection, IR is per 100 person-years, NR= Non-reportable. In both groups, no hospitalization due to tuberculosis and viral hepatitis was noted.

a Incidence rate (IR) is per 100 person-years

b Rate difference per 100 patients (Tocilizumab-Abatacept)

**Supplemental Table 4. Risk of composite serious infections: as-treated analyses with varying maximum follow-up windows.**

|  |  |  |
| --- | --- | --- |
|  | **Tocilizumab**  **(N=16,074)** | **TNF inhibitors**  **(N=33,109)** |
| *Maximum follow-up days* | Combined HR  (95% CI) |  |
| *30 days* | 1.41 (1.02, 1.95) | References |
| *90 days* | 1.07 (0.89, 1.27) | References |
| *180 days* | 1.04 (0.91, 1.20) | References |
| *365 days* | 1.11 (0.99, 1.25) | References |
|  | **Tocilizumab**  **(N=10,414)** | **Abatacept**  **(N=10,414)** |
| *Maximum follow-up days* | Combined HR  (95% CI) |  |
| *30 days* | 1.77 (1.07, 2.93) | References |
| *90 days* | 1.55 (1.18, 2.03) | References |
| *180 days* | 1.35 (1.10, 1.67) | References |
| *365 days* | 1.42 (1.20, 1.69) | References |

TNFi=tumor necrosis factor inhibitor, HR=hazard ratio, CI=confidence interval

**Supplemental Table 5. Combined primary and secondary outcomes (defined using discharge diagnosis at any position): Propensity score-matched as-treated analyses.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Tocilizumab**  **(N=16,074)** | | | **TNF inhibitors**  **(N=33,109)** | | |  |  |
|  | **Events** | **Person-years** | **IR a**  **(95%CI)** | **Events** | **Person-years** | **IR a**  **(95%CI)** | **HR**  **(95%CI)** | **Rate difference b** |
| Composite serious infections | 990 | 13,059 | 7.58  (7.11, 8.05) | 1,868 | 28,620 | 6.53  (6.23, 6.82) | 1.03  (0.95, 1.12) | 1.05  (0.49, 1.61) |
| Serious bacterial infection | 829 | 13,108 | 6.32  (5.89, 6.75) | 1,455 | 28,831 | 5.05  (4.79, 5.31) | 1.12  (1.02, 1.22) | 1.27  (0.77, 1.77) |
| Septicemia/bacteremia | 302 | 13,326 | 2.27  (2.01, 2.52) | 579 | 29,280 | 1.98  (1.82, 2.14) | 1.02  (0.89, 1.18) | 0.29  (-0.01, 0.59) |
| Pneumonia/upper respiratory tract infection | 384 | 13,286 | 2.89  (2.60, 3.18) | 822 | 29,148 | 2.82  (2.63, 3.01) | 0.92  (0.81, 1.04) | 0.07  (-0.28, 0.42) |
| Pyelonephritis/UTI | 339 | 13,271 | 2.55  (2.28, 2.83) | 724 | 29,142 | 2.48  (2.30, 2.67) | 0.89  (0.78, 1.02) | 0.07  (-0.26, 0.40) |
| Opportunistic infection | 55 | 13,400 | 0.41  (0.30, 0.52) | 89 | 29,455 | 0.30  (0.24, 0.36) | 1.17  (0.83, 1.67) | 0.11  (-0.02, 0.24) |
| Skin and soft tissue infection | 68 | 13,411 | 0.51  (0.39, 0.63) | 78 | 29,460 | 0.26  (0.21, 0.32) | 1.83  (1.30, 2.56) | 0.25  (0.12, 0.38) |
| Herpes zoster | 45 | 13,395 | 0.34  (0.24, 0.43) | 76 | 29,433 | 0.26  (0.20, 0.32) | 1.15  (0.78, 1.71) | 0.08  (-0.03, 0.19) |
| Diverticulitis | 90 | 13,395 | 0.67  (0.53, 0.81) | 93 | 29,421 | 0.32  (0.25, 0.38) | 1.93  (1.43, 2.61) | 0.35  (0.20, 0.50) |
| Tuberculosis | NR | 13,421 | 0.00  (0.00, 0.00) | NR | 29,483 | 0.00  (0.00, 0.01) | N/A | - |
| Viral hepatitis | NR | 13,420 | 0.04  (0.00, 0.07) | 41 | 29,457 | 0.14  (0.10, 0.18) | 0.42  (0.16, 1.13) | - |

TCZ=tocilizumab, TNFi=tumor necrosis factor inhibitor, HR=hazard ratio, CI=confidence interval, UTI=urinary tract infection, NR= Non-reportable.

a Incidence rate (IR) is per 100 person-years**.** b Rate difference per 100 patients (Tocilizumab-TNF inhibitors)

In both groups, no hospitalization due to tuberculosis was noted.