**SUPPLEMENTARY DATA**

**Supplemental Table 1: Demographic and Clinical Characteristics at the time of starting TNF inhibitor**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Factor | Overall (n=135) | Discontinuation group | | Continuation group  (n=21, C) | P-value | |
| with GC-free sustained LDA (n=99, A) | without GC -free sustained LDA (n=15, B) |
| A vs B | A vs C |
| Age | 57 [47, 65] | 57 [46, 64] | 54 [43, 68] | 59 [54, 69] | 0.88 | 0.42 |
| Female gender | 108 (80.0) | 82 (82.8) | 9 (60.0) | 17 (81.0) | 0.08 | 0.76 |
| Body mass index | 20.2 [18.7, 22.9] | 20.5 [19.0, 22.9] | 20.9 [18.8, 27.0] | 19.6 [17.3, 21.3] | 0.28 | 0.08 |
| Smoking |  |  |  |  | **0.04** | 0.94 |
| Never | 84 (62.2) | 64 (64.6) | 5 (33.3) | 15 (71.4) |  |  |
| Previous | 29 (21.5) | 19 (19.2) | 7 (46.7) | 3 (14.3) |  |  |
| Current | 22 (16.3) | 16 (16.2) | 3 (20.0) | 3 (14.3) |  |  |
| Symptom duration (month) | 18 [10, 76] | 14 [8, 59] | 59 [12, 167] | 83 [46, 132] | **0.01** | **<0.001** |
| ≤12 months | 54 (40.0) | 47 (47.5) | 4 (26.7) | 3 (14.3) | 0.17 | **<0.01** |
| Interval between starting MTX and TNFi (month) | 8 [4, 32] | 6 [4, 18] | 11 [8, 33] | 32 [8, 69] | 0.06 | **<0.01** |
| Previous biologic use | 18 (13.3) | 8 (8.1) | 1 (6.7) | 9 (42.9) | 1.00 | **<0.001** |
| TJC (in 68 joints) | 10 [6, 15] | 10 [5, 15] | 12 [8, 15] | 10 [5, 14] | 0.23 | 0.99 |
| SJC (in 66 joints) | 10 [5, 16] | 10 [5, 16] | 11 [6, 14] | 10 [5, 16] | 0.92 | 0.92 |
| Pain (0-100 mm) | 53 [30, 70] | 51 [28, 69] | 51 [26, 56] | 69 [51, 79] | 0.56 | **<0.01** |
| PtGA (0-100 mm) | 50 [29.5, 70] | 44 [21, 68] | 51 [45, 60.5] | 60 [50, 77] | 0.35 | **0.01** |
| PhGA (0-100 mm) | 38 [30, 55] | 38 [30, 54] | 39 [35, 59] | 43 [29, 60] | 0.38 | 0.51 |
| HAQ-damage index (0-3) | 0.88 [0.25, 1.62] | 0.75 [0.25, 1.62] | 1.00 [0.25, 1.38] | 1.62 [1.00, 2.00] | 0.88 | **<0.01** |
| ESR (mm/h) | 33 [18, 59] | 32 [18, 64] | 37.5 [21, 50] | 39 [19, 54] | 0.82 | 0.89 |
| CRP (mg/dL) | 0.8 [0.2, 2.0] | 0.7 [0.2, 1.8] | 0.5 [0.2, 1.3] | 1.5 [0.4, 2.2] | 0.40 | 0.34 |
| MMP-3 (ng/mL) | 135 [66, 264] | 127 [57, 256] | 148 [64, 380] | 157 [109, 273] | 0.47 | 0.30 |
| DAS28 | 5.1 [4.3, 5.8] | 5.1 [4.2, 5.8] | 5.1 [4.8, 5.9] | 5.15 [4.8, 6.0] | 0.48 | 0.47 |
| SDAI | 21.8 [15.7, 29.7] | 21.4 [14.6, 30.0] | 26.5 [19.9, 31.9] | 21.8 [17.6, 25.4] | 0.28 | 0.76 |
| RF positive | 110 (81.5) | 82 (82.8) | 11 (73.3) | 17 (81.0) | 0.47 | 0.76 |
| RF titer (U/mL) | 77 [23, 242] | 81 [31, 253] | 43 [18, 186] | 53 [20, 136] | 0.34 | 0.18 |
| ACPA positive | 121 (90.3) | 88 (88.9) | 13 (92.9) | 20 (95.2) | 1.00 | 0.69 |
| SHS | 8 [2, 34] | 6 [2, 18] | 17 [3, 62] | 52 [6, 100] | 0.08 | **<0.01** |
| Erosion score | 3 [0, 13] | 2 [0, 9] | 3 [1, 25] | 18 [3, 53] | 0.39 | **<0.01** |
| JSN score | 5 [0, 19] | 4 [0, 10] | 14 [2, 40] | 21 [3, 65] | 0.04 | **<0.01** |
| MTX | 133 (98.5) | 98 (99.0) | 15 (100.0) | 20 (95.2) | 1.00 | 0.32 |
| MTX (mg/week) | 12 [10, 16] | 12 [10, 16] | 12 [9, 14.5] | 12 [8, 16] | 0.34 | 0.23 |
| Other csDMARD | 12 (8.9) | 6 (6.1) | 1 (6.7) | 5 (23.8) | 1.00 | **0.02** |
| Initial TNFi (%) |  |  |  |  | 0.94 | **0.02** |
| Infliximab | 55 (40.7) | 45 (45.5) | 7 (46.7) | 3 (14.3) |  |  |
| Etanercept | 49 (36.3) | 29 (29.3) | 6 (40.0) | 14 (66.7) |
| Adalimumab | 23 (17.0) | 17 (17.2) | 2 (13.3) | 4 (19.0) |
| Certolizumab pegol | 5 (3.7) | 5 (5.1) | 0 (0.0) | 0 (0.0) |
| Golimumab | 3 (2.2) | 3 (3.0) | 0 (0.0) | 0 (0.0) |
| PSL | 71 (52.6) | 48 (48.5) | 11 (73.3) | 12 (57.1) | 0.10 | 0.63 |
| PSL (mg/day) | 2 [0, 5] | 0 [0, 5] | 3 [0.5, 3] | 2 [0, 5] | 0.38 | 0.37 |
| Self-pay ratio of 0% by medical benefits | 17 (12.6) | 3 (3.0) | 4 (26.7) | 10 (47.6) | **<0.01** | **<0.001** |

Data are represented as the median [interquartile range] or the number (%). P-value of less than 0.05 are represented as bold. Abbreviations: ACPA, anti-cyclic citrullinated peptide antibodies; ACR, American College of Rheumatology; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28, Disease Activity Score in the 28 joints; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; GC, glucocorticoid; HAQ, Health Assessment Questionnaire; LDA, low disease activity; MMP-3, matrix metalloproteinase-3; MTX, methotrexate; PhGA, physician's global assessment for the current disease activity; PtGA, patient's global assessment for the current disease activity; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SHS, van der Heijde-modified Sharp score; SJC, swollen joint count; TJC, tender joint count; TNFi, tumor necrosis factor inhibitor.

**Supplemental table 2: Prevalence of stopping TNF inhibitor after achieving glucocorticoid-free sustained low disease activity and successful TNF inhibitor cessation over one year stratified by symptom duration before starting TNF inhibitor (n=131)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Symptom duration | | | | | | | | | | |
| ≤1 year (n=53) | |  | ≤2 year (n=73) | |  | ≤5 year (n=88) | |  | >5 year (n=43) | |
| Patients without flare over 1 year after TNFi cessation | 37 | 69.8% |  | 49 | 67.1% |  | 59 | 67.0% |  | 10 | 23.3% |
| Patients stopping TNFi after achieving GC-free LDA | 46 | 86.8% |  | 62 | 84.9% |  | 74 | 84.1% |  | 21 | 48.8% |

Four patients who stopped a TNF inhibitor after achieving glucocorticoid-free sustained low disease activity and never received MTX during TNF inhibitor-free period were excluded. Proportions of patients without flare over 1 year after TNFi cessation and those stopping TNFi after achieving GC-free LDA in patients with symptom duration of more than 5 years before starting TNF inhibitor in this study cohort were significantly fewer than those in patients with symptom duration before starting TNFi of 5 years or less (P< 0.001 and P<0.001, respectively). Abbreviations: refer to the footnotes in Supplemental Table 1.

**Supplemental table 3: Clinical and functional remission after TNF inhibitor cessation (n=95)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Month | SDAI | | DAS28 | | ACR/EULAR Boolean remission | HAQ<0.5 |
| LDA | Remission | LDA | Remission |
| 0 | 95/95 (100) | 83/95 (87.4) | 92/95 (96.8) | 80/95 (84.2) | 66/95 (69.5) | 81/95 (85.3) |
| 3 | 81/94 (86.2) | 67/94 (71.3) | 74/94 (78.7) | 54/95 (56.8) | 50/95 (52.6) | 71/95 (74.7) |
| 6 | 72/93 (77.4) | 61/93 (65.6) | 67/93 (72.0) | 56/94 (59.6) | 49/94 (52.1) | 62/93 (66.7) |
| 9 | 67/92 (72.8) | 52/92 (56.5) | 55/92 (59.8) | 52/93 (55.9) | 40/93 (43.0) | 60/91 (65.9) |
| 12 | 64/92 (69.6) | 56/92 (60.9) | 60/92 (65.2) | 50/93 (53.8) | 43/93 (46.2) | 57/91 (62.6) |

We could not follow the five patients for one year after TNFi cessation due to lost to follow up. Three of them were censored without flare at 56, 161, 224 days after TNFi cessation. Their DAS28/SDAI/fulfilment of Boolean definition at their last observations were 2.95/1.91/ No, 2.56/0.44/Yes, 2.14/2.19/No, respectively. The other two had flare with moderate disease activity defined by DAS28 as well as SDAI, and one restarted TNFi therapy. Refer to the text for the definition of handling of missing values.

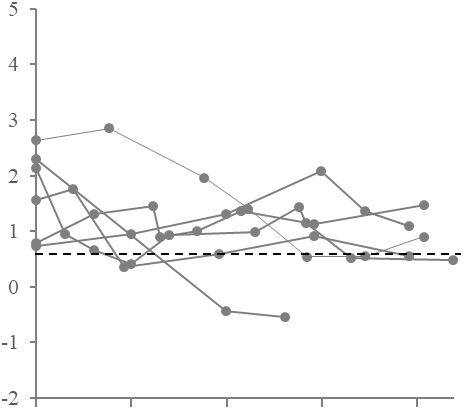
Abbreviations: ACR, American College of Rheumatology; EULAR, European League Against Rheumatism. Other abbreviations: refer to the footnotes in Supplemental Table 1.

**Supplemental table 4: Results of multivariable Cox regression for prediction of disease flare after TNFi cessation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Disease flare | | |  |
| Variables | HR | [95% CI] | P-value |  |
| Age (10-year) | 0.86 | [0.54-1.08] | 0.12 |  |
| Female gender | 11.21 | [1.91-65.97] | <0.01 |  |
| Current smoker | 6.11 | [1.99-18.79] | <0.02 |  |
| Interval between starting MTX and TNFi (month) | 1.02 | [1.00-1.04] | 0.01 |  |
| RF titer at starting TNFi (10 U/mL) | 1.01 | [1.00-1.01] | 0.02 |  |
| SHS total score at starting TNFi (unit) | 0.99 | [0.98-1.01] | 0.28 |  |
| PSL at starting TNFi (mg/day) | 1.11 | [1.01-1.23] | 0.03 |  |
| Time to sustained LDA (month) | 1.01 | [0.99-1.04] | 0.34 |  |
| ΔErosion score during TNFi therapy (unit) | 1.04 | [0.82-1.33] | 0.73 |  |
| HAQ at TNFi cessation (unit) | 2.24 | [1.03-4.87] | 0.04 |  |

Abbreviations: refer to the footnotes in Supplemental Table 1.

**Supplemental figure 1: Regained disease control after the flare**



ΔDAS28

0

12

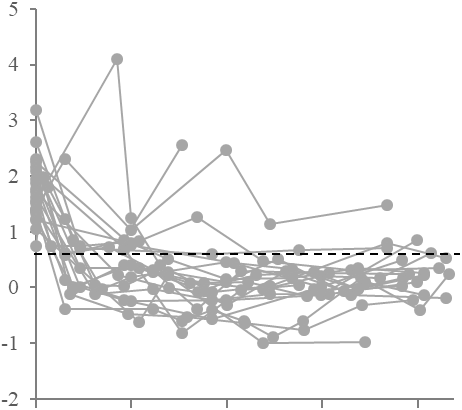
9

6

3

B. Patients who did not restart TNFi

Months after the flare



ΔDAS28

0

12

9

6

3

A. Patients who restarted TNFi **inhibitors**

Months after the flare

ΔDAS28 indicates amount of change in DAS28 value from the mean AUC value of DAS28 for 6 months before TNFi cessation. Dashed horizontal lines indicate the mean AUC value of DAS28 for 6 months before TNFi cessation + 0.6. Abbreviations: refer to the footnotes in Supplemental Table 1.

**Supplemental figure 2: Prediction model for flare and readministration of TNFi**

**A) Disease flare**

0.89 [0.76-1.00]

Months after cessation of TNFi therapy

Probability of flare-free survival

0

3

6

9

12

0.0

0.2

0.4

0.6

0.8

1.0

0.62 [0.48-0.75]

0.28 [0.07-0.53]

≤1 risk factor (n=28)　　　　2 risk factors (n=51)　　　　3 risk factors (n=16)

Risk factors: female gender, current smoking, interval between starting MTX and TNFi >9 months, prednisolone use at the time of starting TNFi. No patient had all of the four risk factors. Probabilities of no flare at 1 year after TNFi cessation in the risk categories with 95% confidence interval determined by bootstrap resampling were noted.