Online supplement to: Assessments of Risks for Pulmonary Infection During 12 Months Following Immunosuppressive Treatment for Active Connective Tissue Diseases: A Report from a Large-scale Prospective Cohort Study. *The Journal of Rheumatology.* doi:10.3899/jrheum.140778

ONLINE SUPPLEMENTARY DATA

Supplementary Table 1. Types of connective tissue diseases and immunosuppressive treatment eligible for enrollment in the PREVENT cohort[a]**.**

Types of Connective Tissue Diseases
systemic lupus erythematosus, rheumatoid arthritis, vasculitis syndrome[b], dermatomyositis, polymyositis, adult-onset Still's disease, mixed connective tissue disease, systemic sclerosis, Behcet's disease and Sjogren syndrome
Immunosuppressive Treatments[a]
1. Prednisolone or other equivalent corticosteroid
2. Methyl prednisolone pulse therapy
3. Conventional immunosuppressants: methotrexate, leflunomide, cyclophosphamide, tacrolimus, cyclosporin, azathioprine, mycophenolate mofetil and mizoribine
4. Biologics infliximab, etanercept, adalimumab, tocilizumab, abatacept and rituximab[c]

[a] Patients are eligible for enrollment in our study if they were admitted to participating hospitals for treatment of new-onset or relapsed connective tissue diseases and started one of these categories of immunosuppressive treatment. Patients who had been receiving immunosuppressive treatments and were given increased doses of corticosteroid, added mPSL pulse therapy, immunosuppressants or biologics, or changed immunosuppressants or biologics at enrollment were also eligible. [b] Vasculitis syndrome includes microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, polyarteritis nodosa, Takayasu arteritis, giant cell arteritis and unclassified vasculitis. [c] Golimumab and certolizumab pegol were not approved in Japan when this study was implemented. PREVENT: Pulmonary infections in patients REceiving immunosuppressiVE treatmeNT for CTD; mPSL: methyl prednisolone; CTD: connective tissue diseases.

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Supplementary Table 2. Laboratory data at baseline[a]**.** Values are mean ± SD unless otherwise specified.

Variable	Infection Group, n = 61	Noninfection Group, n = 702
Hemoglobin, g/dl	11.1 ± 2.2	11.4 ± 2.0
White blood cell count, /μl	8200 ± 4212	8162 ± 4933
Neutrophil count, /μl	6258 ± 3895, n = 60	6163 ± 4213, n = 692
Lymphocyte count, /μl	1118 ± 785, n = 60	1172 ± 690, n = 692
Platelet count,$\times 10^4$ /μl	25.2 ± 15.6	26.3 ± 11.8
IgG, mg/dl	1684 ± 634, n = 60	1676 ± 706, n = 680
IgA, mg/dl	330 ± 179, n = 60	309 ± 160, n = 656
IgM, mg/dl	128 ± 112, n = 60	135 ± 128, n = 656
Serum albumin, mg/dl	3.15 ± 0.65, n = 60	3.32 ± 0.68, n = 694

[a] Laboratory data at baseline. All laboratory data shown in Supplementary Table 2 were not significantly different between patients who developed (infection group) and did not develop pulmonary infections (noninfection group). Ig: immunoglobulin.

Supplementary Table 3. The use of each conventional immunosuppressant and biologic. Values are n (%).

Treatments	First 14 Days from Baseline[a]	Whole Observation Period[a]
Conventional immunosuppressants		
Cyclophosphamide	97 (12.7)	172 (22.5)
Azathioprine	13 (1.7)	67 (8.8)
Cyclosporin	44 (5.8)	78 (10.2)
Tacrolimus	72 (9.4)	148 (18.7)
Methotrexate	122 (16.0)	163 (21.4)
Mizoribine	7 (0.9)	14 (1.8)
Mycophenolate mofetil	1 (0.1)	1 (0.1)
Biologics		
Infliximab	53 (6.9)	75 (9.8)
Etanercept	27 (3.5)	44 (5.8)
Adalimumab	23 (3.0)	30 (3.9)
Tocilizumab	29 (3.8)	52 (6.8)
Abatacept	0 (0)	4 (0.5)
Rituximab	5 (0.7)	5 (0.7)

[a] Use of each immunosuppressive treatment is counted if patients are given each treatment at least 1 dose.

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Supplementary Table 4. Comparison of baseline characteristics and medications of patients in the NCC study[a]. Values are mean ± SD or % unless otherwise stated.

Characteristics	Case Group, n = 60	Control Group, n = 120	p
Baseline characteristics			
Age, yrs	65.5 ± 12.9	65.5 ± 12.9	0.94
Female sex	63.3	63.3	1.00
Body weight, kg	52.8 ± 9.8	52.6 ± 9.7	0.77
Disease duration, mos	42.8 ± 76.3	56.3 ± 95.6	0.31
Incident use of immunosuppressive therapy	65.0	51.7	0.09
Ever smoker	45.0	37.5	0.33
≥ 20 pack-years of smoking[b]	40.0	28.3	0.11
Concurrent non-serious infection (%)	5.0	4.2	0.80
Resolved serious infection within 6 mos	5.0	2.5	0.38
Performance status ≥ 3[c]	23.3	15.0	0.17
Dysphagia	5.0	1.7	0.20
Heart failure	6.7	1.7	0.08
Diabetes mellitus	25.0	20.8	0.53
Previous pulmonary tuberculosis[d]	15.0	11.7	0.53
Any pulmonary comorbidity	60.0	50.8	0.25
Serum creatinine, mg/dl	1.09 ± 1.36	0.85 ± 0.92	0.39
Serum albumin, mg/dl	3.15 ± 0.65, n = 59	3.25 ± 0.60	0.30
Pneumococcal vaccine[e]	6.7	10.0	0.46
Influenza vaccine[f]	25.0	25.0	1.00
Medication during the 14 days at the end of the observation period for NCC in each pair			
Maximum PSL dose, mg/kg/day[g]	0.55 ± 0.30	0.44 ± 0.28	0.02
Use of ≥ 0.5 mg/kg/day of PSL, yes[h]	53.3	34.2	0.01
Use of mPSL pulse therapy, yes[h]	3.3	5.0	0.61
Use of conventional immunosuppressants[i], yes[h]	55.0	48.3	0.40
Use of biologics[j], yes[h]	13.3	10.8	0.62

[a] For each patient who developed PI (case group), two age-, gender-, and disease-matched control patients without pulmonary infection (control group) were selected from the PREVENT cohort. The detailed method for selection of the control group for the NCC study is described in Materials and Methods. We could not select age-, sex-, and disease-matched control patients for 1 of 61 patients with PI (Table 1);

that patient was excluded from the NCC study. The Mann-Whitney U test was used for continuous measures, and the chi-square test for categorical measures. Corrections for multiple comparisons were not made and p values were provided to show magnitude of difference between the 2 groups. [b] Pack-years of smoking mean (packs smoked per day) × (yrs as a smoker). [c] Performance status was evaluated using the Eastern Cooperative Oncology Group performance status. [d] Previous pulmonary tuberculosis includes suspected case. [e] Patients who were given pneumococcal vaccine before enrollment and during the observation period were included in calculation of percentages. Patients who were given pneumococcal vaccine after development of PI were excluded from the calculation. [f] Patients who were given influenza vaccine within 6 months before enrollment and during the observation period were included in calculation of percentages. Patients who were given influenza vaccine after development of PI were excluded from the calculation. [g] Maximum PSL dose during the 14 days at the end of the observational period for the NCC study. The dose of corticosteroids other than PSL was substituted for the equivalent dose of PSL for analysis[23]. [h] Use of mPSL pulse therapy, conventional immunosuppressants and biologics during thw 14 days at the end of the observational period for the NCC study. [i] Including methotrexate, leflunomide, cyclophosphamide, tacrolimus, cyclosporin, azathioprine, mycophenolate mofetil, and mizoribine. [j] Including infliximab, etanercept, adalimumab, tocilizumab, abatacept, and rituximab. NCC: nested case-control; PSL: prednisolone; mPSL: methyl prednisolone.
PI; pulmonary infection.

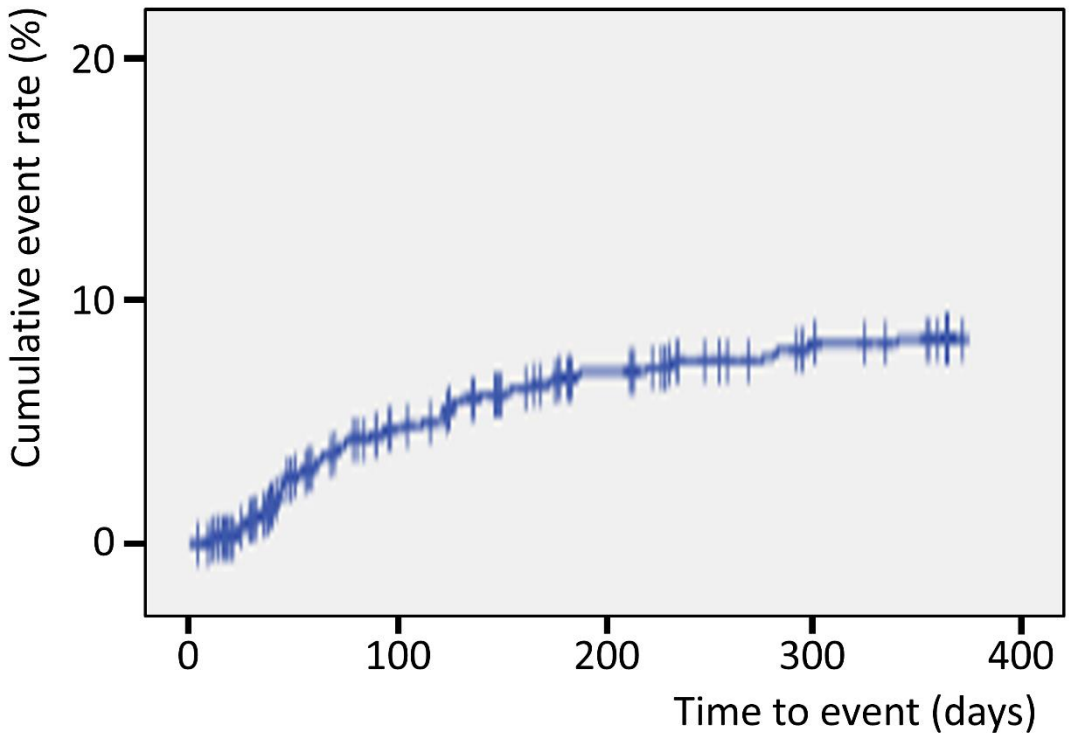
Supplementary Table 5. Multivariate analysis of independent risk factors for PI in patients excluding patients with articular RA[a].

Variable	HR	95% CI	p
Age ≥ 65 years, vs < 65)	4.13	2.32–7.35	< 0.001[c]
Incident use of immunosuppressive therapy	1.42	0.80–2.52	0.231
≥ 20 pack-yrs of smoking, vs < 20	2.73	1.39–5.35	0.004[c]
Serum creatinine, mg/dl	1.23	1.06–1.43	0.006[c]
Performance Status ≥ 3, vs ≤ 2	1.94	1.05–3.57	0.033
Maximum PSL dose, mg/kg/day [b]	2.08	0.83–5.21	0.119

[a] The HR for development of PI of each variable was calculated using the Cox proportional hazard regression model after adjusting for sex. [b] Maximum PSL dose during the first 14 days of immunosuppressive therapy. The dose of corticosteroids other than PSL was substituted for the equivalent dose of PSL for analysis[23]. [c] These p values were statistically significant after corrections for multiple comparisons using False Discovery Rate and Benjamini-Hochberg procedure[24]. In this analysis, maximum dose of PSL showed similar HR to Table 4, but did not reach statistical significance. This could

be explained by skewed distribution of maximum dose of PSL in this population. Median dose (quartiles) of PSL in patients excluding articular RA was 0.93 (0.63–1.03) mg/kg/day. In the cohort where most of the patients were given more than medium dose (i.e., 0.5 mg/kg/day) of PSL, risks of patients' backgrounds (i.e., age, smoking, and renal function) became more conspicuous rather than the risk of daily PSL dose for development of pulmonary infection. Another model that included CTD diagnosis showed essentially the same results. PI: pulmonary infections; RA: rheumatoid arthritis; PSL: prednisolone; mPSL: methyl prednisolone; CTD: connective tissue diseases.

Supplementary Figure 1. The cumulative event curve for occurrence of PI in patients in the PREVENT cohort.



The cumulative event curve for occurrence of the PREVENT cohort is shown. The slope is steep during the first 3 months, becoming more gradual with time. Thirty-three patients (54.1%) developed PI during the first 3 months. PI: pulmonary infections; PREVENT: Pulmonary infections in patients REceiving immunosuppressiVE treatmeNT for CTD; CTD: connective tissue diseases.