Supplementary Material

Treatment Status and Healthcare Cost Trends for Patients with Multiple Sclerosis in Japan: A Claims Database Analysis

Author details:

Izumi Kawachi\(^1,2\), Hiromichi Otaka\(^3\)*, Kosuke Iwasaki\(^4\), Tomomi Takeshima\(^4\), Kengo Ueda\(^3\)

\(^1\)Department of Neurology, Brain Research Institute, Niigata University, 1-757 Asahimachidori, Chuo-ku, Niigata, Japan

\(^2\)Comprehensive Medical Education Center, Niigata University School of Medicine, 1-757 Asahimachidori, Chuo-ku, Niigata, Japan

\(^3\)Neuroscience Medical Franchise, Medical Division, Novartis Pharma K.K., 1-23-1 Toranomon, Minato-ku, Tokyo, Japan

\(^4\)Milliman Inc., 1-6-2 Kojimachi, Chiyoda-ku, Tokyo, Japan

Correspondence details:

Hiromichi Otaka

Neuroscience Medical Franchise, Medical Division, Novartis Pharma K.K., 1-23-1 Toranomon, Minato-ku, Tokyo, Japan

Email: hiromichi.otaka@novartis.com
**Table S1. Classification and definition of treatments**

| Classification     | Treatment name                  | Definition*                                                                 |
|--------------------|---------------------------------|-----------------------------------------------------------------------------|
| DMT                | Interferon -ß1a                 | Interferon Beta-1a (Genetical Recombination)                                |
|                    | Dimethyl fumarate               | Dimethyl Fumarate                                                           |
|                    | Interferon-ß1b                  | Interferon Beta-1b (Genetical Recombination)                                |
|                    | Glatiramer acetate              | Glatiramer Acetate                                                          |
|                    | Fingolimod hydrochloride        | Fingolimod Hydrochloride                                                    |
|                    | Natalizumab                     | Natalizumab (Genetical Recombination)                                       |
| Oral steroid       | Prednisolone                    | Excluding prednisolone prescribed within 3 months of prescription of other relapse treatment drug(s) |
| Immunosuppresant   | Azathioprine                    | Azathioprine                                                                |
|                    | Tacrolimus Hydrate              | Tacrolimus Hydrate                                                          |
|                    | Ciclosporin                     | Ciclosporin                                                                 |
|                    | Mycopenolate Mofetil            | Mycopenolate Mofetil                                                        |
|                    | Cyclophoshamide Hydrate         | Cyclophoshamide Hydrate                                                     |
|                    | Methotrexate                    | Methotrexate                                                                |
|                    | Mitoxantrone Hydrochloride      | Mitoxantrone Hydrochloride                                                  |
| Relapse treatment  | Prednisolone                    | Prednisolone prescribed within 3 months of prescription with other relapse treatment drug(s) |
|                    | Prednisolone Sodium Succinate   | Prednisolone Sodium Succinate                                               |
|                    | Dexamethasone Sodium Phosphate  | Dexamethasone Sodium Phosphate                                              |
|                    | Methylprednisolone Sodium Succinate | Methylprednisolone Sodium Succinate                                         |
|                    | plasma purification therapy     | J039, J041                                                                  |

*General name for drugs or procedure price table code for procedures.

DMT: disease-modifying therapy
Table S2. Definition of comorbidities

| Disease Name                                         | Definition (ICD-10 code) |
|------------------------------------------------------|---------------------------|
| Constipation                                         | K59.0                     |
| Polyneuropathy, unspecified                          | G62.9                     |
| Depressive episode, unspecified                      | F32.9                     |
| Epilepsy, unspecified                                | G40.9                     |
| Neuromuscular dysfunction of bladder, unspecified    | N31.9                     |
| Headache                                             | R51                       |
| Dizziness and giddiness                              | R42                       |
| Rheumatoid arthritis, unspecified                    | M06.9                     |
| Other epilepsy                                       | G40.8                     |
| Generalized anxiety disorder                         | F41.1                     |
| Migraine, unspecified                                | G43.9                     |
| Neurotic disorder, unspecified                       | F48.9                     |
| Sicca syndrome                                       | M35.0                     |
| Trigeminal neuralgia                                 | G50.0                     |

ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision
### Table S3. Definition of clinical tests

| Name of clinical test                                      | Definition (procedure price table code) |
|------------------------------------------------------------|-----------------------------------------|
| MRI                                                        | E202                                    |
| clinical psychological or neuropsychological test          | D283-D285                               |
| neurological test                                         | D239-3                                  |
| ophthalmologic test                                       | D255-D282-3                             |
| cerebrospinal fluid test                                  | D403                                    |
| visual evoked potential test                              | D2362                                   |
| somatosensory evoked potential test                       | D2361                                   |

MRI: magnetic resonance imaging.
Figure S1. Treatment pattern by age (2017)

The percentage for no treatment refers to the percentage of patients without any treatment listed below per patient month, and for each treatment per patient per month.

"Oral steroid is prednisolone excluding those prescribed within 3 months of prescription with other relapse treatment drug(s) than prednisolone.

The colors are assigned for all drugs as below.

| Age       | ~9  | 10~19 | 20~29 | 30~39 | 40~49 | 50~59 | 60~69 | 70~79 | 80~89 | 90~  |
|-----------|-----|-------|-------|-------|-------|-------|-------|-------|-------|------|
| Number of patients (patient month): denominator | 175 | 846   | 3502  | 8568  | 13955 | 10890 | 8069  | 5098  | 1606  | 136  |
| No treatment | No treatment patients | 64.6% | 71.3% | 65.2% | 65.2% | 64.6% | 70.1% | 74.4% | 83.4% | 88.7% | 97.1% |
| DMT       |     |       |       |       |       |       |       |       |       |      |
| Dimethyl fumarate | 0.000 | 0.052 | 0.117 | 0.075 | 0.068 | 0.059 | 0.020 | 0.009 | 0.002 | 0.000 |
| IFN-ß1a   | 0.320 | 0.025 | 0.059 | 0.062 | 0.062 | 0.058 | 0.025 | 0.004 | 0.000 | 0.000 |
| IFN-ß1b   | 0.000 | 0.024 | 0.043 | 0.046 | 0.054 | 0.049 | 0.035 | 0.012 | 0.001 | 0.000 |
| Glatiramer acetate | 0.000 | 0.040 | 0.021 | 0.029 | 0.018 | 0.016 | 0.004 | 0.000 | 0.000 | 0.000 |
| Fingolimod | 0.000 | 0.040 | 0.130 | 0.126 | 0.148 | 0.093 | 0.050 | 0.012 | 0.002 | 0.000 |
| Natalizumab | 0.000 | 0.025 | 0.014 | 0.013 | 0.009 | 0.009 | 0.003 | 0.000 | 0.000 | 0.000 |
| DMT total  | 0.320 | 0.206 | 0.383 | 0.352 | 0.360 | 0.284 | 0.136 | 0.037 | 0.005 | 0.000 |
| Oral steroid | Predonisolone | 0.246 | 0.143 | 0.062 | 0.119 | 0.118 | 0.157 | 0.222 | 0.184 | 0.119 | 0.000 |
| Oral steroid total | 0.246 | 0.143 | 0.062 | 0.119 | 0.118 | 0.157 | 0.222 | 0.184 | 0.119 | 0.000 |
| Immunosuppresant | Azathioprine | 0.183 | 0.000 | 0.014 | 0.007 | 0.018 | 0.023 | 0.025 | 0.009 | 0.000 | 0.000 |
| Tacrolimus | 0.000 | 0.053 | 0.013 | 0.013 | 0.008 | 0.016 | 0.036 | 0.018 | 0.019 | 0.000 |
| Cyclosporine | 0.000 | 0.000 | 0.000 | 0.004 | 0.004 | 0.006 | 0.009 | 0.001 | 0.006 | 0.000 |
| Mycophenolate mofetil | 0.000 | 0.011 | 0.003 | 0.006 | 0.000 | 0.005 | 0.002 | 0.000 | 0.000 | 0.000 |
| Cyclophosphamide | 0.000 | 0.012 | 0.009 | 0.000 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.000 |
| Methotrexate | 0.000 | 0.000 | 0.000 | 0.001 | 0.002 | 0.018 | 0.018 | 0.006 | 0.011 | 0.000 |
| Mitoxantrone | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Immunosuppresant total | 0.183 | 0.076 | 0.041 | 0.031 | 0.033 | 0.068 | 0.091 | 0.035 | 0.037 | 0.000 |
| Relapse treatment drugs | Prednisolone (relapse therapy) | 0.149 | 0.183 | 0.095 | 0.084 | 0.061 | 0.052 | 0.059 | 0.063 | 0.017 | 0.044 |
| prednisolone sodium succinate | 0.006 | 0.018 | 0.007 | 0.006 | 0.006 | 0.003 | 0.007 | 0.006 | 0.000 | 0.000 |
| Dexamethasone phosphate ester sodium | 0.000 | 0.009 | 0.000 | 0.004 | 0.001 | 0.005 | 0.023 | 0.028 | 0.006 | 0.000 |
| Methylprednisolone sodium ester succinate | 0.171 | 0.136 | 0.160 | 0.107 | 0.094 | 0.057 | 0.033 | 0.025 | 0.016 | 0.081 |
| Relapse treatment drugs total | 0.326 | 0.346 | 0.262 | 0.201 | 0.162 | 0.118 | 0.122 | 0.122 | 0.039 | 0.125 |
| Relapse treatment | Plasma purification therapy | 0.000 | 0.000 | 0.012 | 0.003 | 0.002 | 0.004 | 0.004 | 0.001 | 0.001 | 0.000 |

DMT: disease-modifying therapy, IFN: interferon
**Figure S2.** Prevalence of comorbidities by age (2017)

The colors are assigned as below.

![Color Scale]

| Age          | 0  | 10–19 | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | 80–89 | 90– |
|--------------|----|-------|-------|-------|-------|-------|-------|-------|-------|-----|
| Number of patients (patient month): denominator | 175 | 846  | 3502  | 8568  | 13955 | 10890 | 8069  | 5098  | 1606  | 136 |
| Constipation | 9.1% | 8.0% | 7.0%  | 13.3% | 18.0% | 21.4% | 28.1% | 28.9% | 29.0% | 11.0% |
| Polynuropathy, unspecified | 1.7% | 3.7% | 7.3%  | 9.9%  | 13.8% | 15.1% | 17.7% | 14.9% | 13.9% | 14.7% |
| Depressive episode, unspecified | 0.0% | 0.8% | 5.3%  | 6.2%  | 9.3%  | 10.4% | 11.7% | 7.8%  | 7.2%  | 0.0% |
| Epilepsy, unspecified | 2.9% | 6.7% | 6.7%  | 5.7%  | 7.0%  | 9.6%  | 9.2%  | 8.3%  | 5.2%  | 1.5% |
| Neuromuscular dysfunction of bladder, unspecified | 0.0% | 1.4% | 1.4%  | 3.8%  | 5.1%  | 8.0%  | 9.0%  | 8.9%  | 10.5% | 8.8% |
| Headache | 12.0% | 5.8% | 9.9%  | 8.5%  | 7.8%  | 6.6%  | 4.7%  | 3.3%  | 1.9%  | 0.0% |
| Dizziness and giddiness | 0.0% | 3.1% | 3.7%  | 4.1%  | 5.1%  | 4.9%  | 5.0%  | 6.0%  | 2.4%  | 0.0% |
| Rheumatoid arthritis, unspecified | 0.0% | 0.6% | 0.9%  | 1.8%  | 3.1%  | 4.4%  | 6.4%  | 6.3%  | 5.9%  | 1.5% |
| Other epilepsy | 5.1% | 4.4% | 2.5%  | 2.7%  | 2.9%  | 3.8%  | 3.6%  | 3.5%  | 2.1%  | 0.0% |
| Generalized anxiety disorder | 0.0% | 3.1% | 1.9%  | 2.8%  | 3.1%  | 3.4%  | 4.7%  | 3.5%  | 2.1%  | 0.0% |
| Migraine, unspecified | 0.0% | 3.4% | 4.7%  | 3.6%  | 3.4%  | 3.6%  | 1.8%  | 1.2%  | 0.2%  | 0.0% |
| Neurotic disorder, unspecified | 0.0% | 0.0% | 0.6%  | 2.5%  | 2.7%  | 2.4%  | 3.3%  | 2.0%  | 2.7%  | 0.0% |
| Sicca syndrome | 0.0% | 1.4% | 0.9%  | 1.3%  | 2.6%  | 2.3%  | 3.9%  | 2.7%  | 2.7%  | 0.0% |
| Trigeminal neuralgia | 0.0% | 0.0% | 0.8%  | 1.1%  | 1.8%  | 2.7%  | 4.0%  | 2.3%  | 0.9%  | 0.0% |
**Figure S3.** Healthcare resource utilization and healthcare costs by age (2017)

The colors are assigned by each item group (clinical tests, hospitalization, relapse, hospital visit, or healthcare costs) as below.

| Age | ~9  | 10~19 | 20~29 | 30~39 | 40~49 | 50~59 | 60~69 | 70~79 | 80~89 | 90~ |
|-----|-----|-------|-------|-------|-------|-------|-------|-------|-------|------|
| Number of patients (patient month): denominator | 175 | 846 | 3502 | 8568 | 13955 | 10890 | 8069 | 5098 | 1606 | 136 |
| Clinicial tests (PPPM) | MRI | 0.291 | 0.294 | 0.240 | 0.205 | 0.185 | 0.147 | 0.110 | 0.084 | 0.057 | 0.059 |
| | Clinical psychological or neuropsychological test | 0.011 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.008 | 0.000 |
| | Neurological test | 0.000 | 0.004 | 0.008 | 0.006 | 0.004 | 0.004 | 0.002 | 0.001 | 0.000 | 0.000 |
| | Ophthalmologic test | 0.549 | 0.755 | 0.371 | 0.313 | 0.346 | 0.320 | 0.378 | 0.377 | 0.270 | 0.015 |
| | Cerebrospinal fluid test | 0.023 | 0.026 | 0.021 | 0.012 | 0.009 | 0.006 | 0.007 | 0.010 | 0.009 | 0.007 |
| | Visual evoked potential test | 0.000 | 0.006 | 0.007 | 0.004 | 0.002 | 0.002 | 0.001 | 0.001 | 0.000 | 0.000 |
| | Somatosensory evoked potential test | 0.000 | 0.012 | 0.006 | 0.005 | 0.003 | 0.003 | 0.001 | 0.002 | 0.000 | 0.000 |
| Hospitalization (PPPM) | Hospitalization | 0.057 | 0.059 | 0.033 | 0.028 | 0.024 | 0.025 | 0.032 | 0.040 | 0.045 | 0.066 |
| Relapse (PPPM) | Relapse | 0.023 | 0.039 | 0.039 | 0.029 | 0.027 | 0.021 | 0.016 | 0.015 | 0.009 | 0.015 |
| Hospital visit (PPPM) | Hospital visit | 0.771 | 0.758 | 0.792 | 0.786 | 0.884 | 0.834 | 0.921 | 0.962 | 0.822 | 0.640 |
| Healthcare costs (JPY, PPPM) | Total healthcare costs | 96,475 | 138,026 | 114,216 | 122,478 | 116,799 | 102,481 | 88,618 | 72,789 | 78,541 | 68,576 |
| | MS treatment cost | 40,866 | 41,526 | 81,337 | 84,107 | 82,010 | 55,568 | 28,783 | 10,449 | 3,802 | 64 |
| | Clinical test cost | 3,627 | 4,112 | 3,086 | 2,626 | 2,438 | 2,010 | 1,667 | 1,411 | 995 | 848 |
| | Other healthcare costs | 51,982 | 92,388 | 29,793 | 35,744 | 32,351 | 44,903 | 58,169 | 60,929 | 73,743 | 67,664 |

JPY: Japanese yen, MRI: magnetic resonance imaging, MS: multiple sclerosis, PPPM: per patient per month.