# Sjögren's syndrome: managed care data from a large United States population highlight real-world health care burden and lack of treatment options

J.A. Birt[1], Y. Tan[2], N. Mozaffarian[2]

*[1]Lilly Corporate Center, Indianapolis, Indiana; [2]Lilly Biotechnology Center, San Diego, California, USA.*

## Abstract

### Objective

*To better understand the real-world characteristics and costs of Sjögren's syndrome (SS).*

### Methods

*Analysing the MarketScan Commercial Claims database from Jan. 1, 2006 to Dec. 31, 2011, we identified 10,414 patients ≥18 years old newly diagnosed with SS. Patient characteristics, drugs (commonly used for SS), resource utilisation, and medical costs were evaluated for 12 months pre- and post-diagnosis.*

### Results

*Mean age was 55 years; 90% were female. At diagnosis, SS patients were most often seen by rheumatologists (39%) or internists (14.2%); the most common concurrent autoimmune conditions were rheumatoid arthritis (17.9%) and systemic lupus erythematosus (14.6%). Other common comorbidities were hypertension (37.6%), osteoarthritis (31.4%), and hyperlipidaemia/dyslipidaemia (30.3%). Post diagnosis of SS, claims for myocardial infarction and coronary artery bypass graft doubled. Medications of interest prescribed post-diagnosis were eye/mouth drugs (32.2%) and synthetic immunosuppressants (32.1%). Biologic drugs were prescribed to a minority (TNF inhibitors, ~5.0%; non-TNF inhibitors, 1%). Of note, prescriptions for all systemic immunotherapies (synthetic and biologic) were significantly lower in the subgroup without concurrent autoimmune disease, and 15.1% of the overall population had no SS-related prescriptions. Post diagnosis, total medical resource utilisation and total medical costs increased (1.2 and 1.4-fold, respectively).*

### Conclusion

*In this retrospective, real-world analysis, medical claims in the first year after SS diagnosis revealed that cardiovascular (CV) events increased and all-cause healthcare costs grew by 40%. Pharmacologic management consisted primarily of low potency immunomodulation and symptomatic treatments. Systemic disease-modifying therapies were used mostly in patients who had another concurrent autoimmune disease, suggesting a lack of treatment options for SS.*

**Key words**

Sjögren's syndrome, drug utilisation, health care costs, insurance claim reporting, autoimmunity, cardiovascular diseases, anti-rheumatic agents, biological products

*Julie A. Birt, PharmD*
*YingMeei Tan, PhD*
*Neelufar Mozaffarian, MD, PhD*

*Please address correspondence to:*
*Julie A. Birt,*
*Lilly Corporate Center,*
*Eli Lilly and Company,*
*Indianapolis, IN 46285, USA.*
*E-mail: j.birt@lilly.com*

*Received on March 7, 2016; accepted in revised form on July 11, 2016.*



*Competing interests: all the authors are employees and/or stock holders of Eli Lilly and Company.*

## Introduction

Sjögren's syndrome (SS) is estimated to be the second most common autoimmune rheumatic disease, with a reported prevalence of 0.03%–2.7% worldwide (1). This wide-ranging prevalence arises from the different classification criteria used to characterise SS. There have been limited studies on SS prevalence in the United States, though an administrative claims database analysis reported a prevalence of SS in the US of 0.06% identified by International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 710.2 (2). The terminology of primary and secondary SS (*i.e.* SS occurring without and with another concurrent autoimmune disease, respectively) is well-entrenched in the literature; however, the medical community is moving away from this arbitrary categorisation (3). This departure from the labels of primary *versus* secondary SS is also supported by the Sjögren's Syndrome Foundation (SSF) (4). Therefore, we have avoided these terms in the analyses presented here.

Sjögren's syndrome is an exocrinopathy with hallmark features of oral and ocular dryness; xeroses can also involve the nose, pharynx, and vagina. Sequelae include corneal ulceration, difficulty chewing, swallowing, and speaking, increased risk of dental caries, and other infections (5). Extraglandular features, such as disabling fatigue, arthralgias, myalgias, neuropathies, pulmonary, renal, and hepatic disorders have been reported in 30%–70%, with more severe symptoms manifesting in 20%–40% (6-10). Lymphoma has been reported to occur in 2–9% of SS patients (11).

The deleterious effect of SS on quality of life is comparable to that experienced by patients with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) (12, 13). Data from a postal survey of 277 US patients with physician-diagnosed SS found that, compared to healthy controls, SS patients were significantly more likely to be unemployed due to disability (12% *vs*. 0%; $p<0.05$), to have been hospitalised during the previous 5 years (53% *vs*. 40%; $p<0.05$) and to have visited healthcare providers, including rheumatologists (94% *vs*. 13%; $p<0.05$), ophthalmologists (79% *vs*. 51%; $p<0.05$), and neurologists (49% *vs*. 16%; $p<0.05$) (14).

Given the systemic impact of SS, the healthcare burden is speculated to be quite large; however, published information regarding SS healthcare utilisation and costs in the US is scant; reported SS costs are limited to data for the United Kingdom (UK) (15, 16). Callaghan and colleagues evaluated healthcare resource usage and direct costs of 129 female pSS patients compared with age-matched females with rheumatoid arthritis, and a control group. Mean annual direct healthcare costs for cost year 2004/2005 were £2,188 ($4,010) per patient in the SS group, £2,693 ($4,940) per patient in the RA group, and £949 ($1,740) per person in the control group. Costs for total healthcare professional visits (£1,182 [$2,170]), dental visits (£452 [$779]), and ophthalmologist visits (£66 [$121]) were higher for SS patients compared to RA patients (£849 [$1,560], £165 [$302], £15 [$27.50], respectively, and the control group (£603 [$1,110]), £302 [$554]), £23 [$42.20]), respectively. The SF-36 physical function subscale was identified as the best predictor of costs in the SS group, via regression analysis (15). Indirect costs for SS patients were estimated to be up to 83% of the indirect costs associated with RA: £13,502 ($25,000) for SS patients, £17,070 ($31,700) for RA patients, and £3,382 ($6,270) for community controls (16).

Published data on SS patient characteristics and prescription patterns in the US are also lacking. Pharmacologic management of ocular SS typically involves treatment with artificial tears and may include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid, or cyclosporine-containing eye drops. Treatment of dry mouth typically starts with saliva substitutes and mouthwashes/oral pastes, and progresses to secretagogues. For mild-moderate extraglandular symptoms, hydroxychloroquine and low-dose steroids may be used, although recent data suggest a lack of efficacy of hydroxychloroquine for dryness, pain and fatigue in SS (17). More potent immunosuppressive thera-

**Table I.** Patient selection: Sjögren's syndrome patients.

| Patient selection: Sjögren's syndrome | Total |
|---|---|
| Patients with an ICD-9 code of 710.2 between January 1, 2006 and December 31, 2011 | 111194 |
| Sjögren's syndrome patients with continuous pharmaceutical and medical benefit enrolment for 1 year prior to and 1 year post the index date (allow a 30 day gap) | 34130 |
| Sjögren's syndrome patients with 2 outpatient diagnosis claims (on different days) or one inpatient diagnosis for Sjögren's Syndrome (ICD-9: 710.2) during the study period (index and post period) | 11477 |
| Patients >18 years old | 11385 |
| Newly diagnosed | 10414 |

**Table II.** Sjögren's syndrome patients: demographics.

| Demographic category | Sjögren's syndrome patients n=10,414 n (%) |
|---|---|
| Female sex | 9,376 (90.0) |
| Age at index date | |
| Mean age (median) years | 54.8 (55.0) |
| Range | 18.0-99.0 |
| <39 years | 1,312 (12.6) |
| 40-50 years | 2,388 (22.9) |
| 51-61 years | 3,906 (37.5) |
| 62-72 years | 1,702 (16.3) |
| 73 years+ | 1,106 (10.6) |
| Physician Specialty at index date | |
| Rheumatology | 4,062 (39.0) |
| Internal medicine | 1,475 (14.2) |
| Medical doctor (not elsewhere classified) | 736 (7.1) |
| Family practice | 714 (6.9) |
| Ophthalmology | 639 (6.1) |
| Otolaryngology | 307 (2.9) |
| Unknown | 334 (3.2) |
| Combination of all other subspecialties | 2,147 (20.6) |

pies (*e.g.* azathioprine or methotrexate) may be prescribed for more significant arthritis, neuropathy, or interstitial lung disease, and severe disease, such as progressive sensorimotor neuropathy, may require cyclophosphamide and intravenous steroids (18, 19). Studies have shown little benefit for tumour necrosis factor (TNF) inhibitors in SS (20-22), but B-cell targeted therapies may be promising (18).

To better understand real-world patient characteristics, current treatments, and potential unmet needs in this population, we examined data from a large, US administrative claims database to identify patients newly diagnosed with SS. Here we summarise our findings, including patient demographics, concomitant medical conditions, treatment patterns, healthcare resource utilisation and costs, and highlight the learnings from these analyses.

## Materials and methods

### *Data source*

This retrospective, observational study was performed using the Truven MarketScan Commercial Claims and Medicare Supplemental Benefits databases, during the period of January 1, 2006 to December 31, 2011 (observation period). These databases capture person-specific clinical utilisation, expenditures, and enrollment across the full continuum of care in all settings, inpatient, outpatient, prescription drug, and carve-out (*e.g.* mental health) services from a selection of large employers, health plans, and government and public organisations in the US. Data from individual patients are integrated from all providers of care. They link paid claims and encounter data to detailed patient information and types of providers, and include private-sector health data from approximately 100 payers and several million individuals annually (23).

### *Sample selection*

For inclusion in this study, patients must have been ≥18 years old with "newly diagnosed" SS, defined as having at least 1 inpatient medical claim or at least 2 outpatient claims for Sicca Syndrome (ICD-9-CM code 710.2), with no prior SS claims during the 12-month pre-index period. This diagnosis code has 95.5% sensitivity and 95.8% specificity for identifying SS when directly compared to a medical chart review (24). The date of the first SS medical claim during the observation period was designated as the index date. Patients without continuous pharmaceutical/medical benefits for 12 months both pre- and post-index were excluded.

### *Outcomes measures*

Demographics, physician specialty associated with the index date, and comorbidities were summarised. Outcomes measured during the 12-month post-period included concurrent diseases, prescribed medications of interest and healthcare utilisation and costs. Corticosteroids were classified as: lower dose (defined as oral or parenteral prednisone ≤20 mg/day or equivalent), higher dose (oral or parenteral prednisone >20 mg/day or equivalent), topical (dermal, nasal and inhalational forms) and ophthalmic (included in "Corticosteroid or NSAID ophthalmic medications"). Data included the total days of supply of each medication and change in use of medications between the pre-index and post-index periods. Healthcare utilisation outcomes included outpatient visits, emergency room (ER) visits, and inpatient admissions. Direct healthcare costs included medical costs (*i.e.* outpatient visits, ER visits, and hospitalisations) and prescription drug costs. Cost analyses were defined as the amount paid by third-party payers, not including out-of-pocket costs, such as deductibles or copayments. Costs accrued during the 1-year post- index period were inflated to 2014 dollars using the medical component of the Consumer Price Index. For both healthcare resource utilisation and costs, both all-cause and SS-associated events were examined. Inpatient costs or resource use were defined as SS-associated when accompanied by a primary diagnosis code of 710.2 (Sicca syndrome), while outpatient costs or resource use were considered SS-associated if the claims had a diagnosis code of 710.2 in any field (primary or secondary).

### *Statistical analyses*

Categorical variables are presented as the count and percentage of patients in each category; continuous variables are summarised as the mean and standard deviation. Prescriptions for drugs

of interest were compared between SS patients with and without additional autoimmune conditions using the Chi Square test. Rates of all-cause and SS-related healthcare utilisations were compared between the pre- and post-index periods using McNemar's test, and healthcare costs were compared using the paired *t*-test.

## Results

*Demographics*

We identified a total of 10,414 patients newly diagnosed with SS between January 1, 2006 and December 31, 2011 (Table I). Their mean age was 54.8 years (± 13.4) and 90% were female. At the index visit, 39% were seen by a rheumatologist, and the next most frequently associated physician specialties were internal medicine, medical doctor, family practice, and ophthalmology (Table II).

*Comorbidities*

Over half (53.9%) of the SS patients had 1 or more additional autoimmune diagnoses during the first year after the index date, while 44.5% had one or more claims for another autoimmune disease before their index date. The most common concurrent autoimmune diseases in the post-period were RA (17.9%) and SLE (14.6%), similar to the pre-period, with 13.3% RA and 10.5% SLE (Table III).

The most prevalent non-autoimmune, medical conditions were hypertension (37.6%), osteoarthritis (31.4%), and hyperlipidaemia/dyslipidaemia (30.3%) (Table IV).

Increased risk of CV disease has been associated with SS. In our study, the following diagnoses were observed during the first year after the index date: CV disease (8.5%), coronary atherosclerosis (7%), cerebrovascular disease (6.8%), major adverse cardiovascular event (MACE) (4.6%), and transient ischaemic attack (TIA)/stroke (3.1%) (Table V). A comparison of the number of patients with CV medical claims during the pre- and post-index periods is shown in Table V; myocardial infarction (MI) and coronary artery bypass graft (CABG) occurred in approximately twice as many patients in the 1-year post-SS diagnosis.

**Table III.** Concurrent autoimmune/inflammatory conditions in the 12-month pre-diagnosis *versus* the 12-month post-diagnosis of Sjögren's syndrome.*

| Autoimmune/Inflammatory condition | Sjögren's syndrome patients: pre-diagnosis n=10,414 n (%) | Sjögren's syndrome patients: post-diagnosis n=10,414 n (%) |
|---|---|---|
| Rheumatoid arthritis | 1,383 (13.3) | 1,862 (17.9) |
| Systemic lupus erythematosus | 1,092 (10.5) | 1,518 (14.6) |
| Unspecified inflammatory polyarthropathy | 534 (5.1) | 682 (6.5) |
| Raynaud's syndrome | 315 (3.0) | 483 (4.6) |
| Eosinophilic and non-infectious gastroenteritis | 319 (3.1) | 360 (3.5) |
| Systemic sclerosis | 199 (1.9) | 308 (3.0) |
| Rheumatism unspecified and fibrositis | 186 (1.8) | 268 (2.6) |
| Other psoriasis and similar | 148 (1.4) | 156 (1.5) |
| Atopic dermatitis and related conditions | 122 (1.2) | 140 (1.3) |
| Psoriatic arthritis | 82 (0.8) | 122 (1.2) |
| Polymyalgia rheumatica | 103 (1.0) | 118 (1.1) |
| Multiple sclerosis | 110 (1.1) | 108 (1.0) |
| Other specific diffuse disease of connective tissue | 60 (0.6) | 105 (1.0) |
| Primary pulmonary hypertension | 48 (0.5) | 101 (1.0) |

*Medical claims in ≧1% of patients.

**Table IV.** Other medical conditions in the 12-month pre-diagnosis *versus* the 12-month post-diagnosis of Sjögren's syndrome.

| Comorbidity | Sjögren's syndrome patients: pre-diagnosis n=10,414 n (%) | Sjögren's syndrome patients: post-diagnosis n=10,414 n (%) |
|---|---|---|
| Hypertension | 3,598 (34.5) | 3,919 (37.6) |
| Osteoarthritis | 2,583 (24.8) | 3,275 (31.4) |
| Hyperlipidaemia/dyslipidaemia | 3,206 (30.8) | 3,156 (30.3) |
| Mental disorders | 2,382 (22.9) | 2,678 (25.7) |
| Chronic lower back pain | 2,198 (21.1) | 2,431 (23.3) |
| Any infectious or parasitic disease | 2,167 (20.8) | 2,325 (22.3) |
| Fibromyalgia | 1,583 (15.2) | 1,844 (17.7) |
| Chronic obstructive pulmonary disease | 1,652 (15.9) | 1,778 (17.1) |
| Diabetes | 1,064 (10.2) | 1,188 (11.4) |
| Osteoporosis | 924 (8.9) | 1,192 (11.4) |
| Cancers | 975 (9.4) | 1,084 (10.4) |

**Table V.** Cardiovascular claims in patients with Sjögren's syndrome in the pre- and post-index periods.

| Cardiovascular conditions | Sjögren's syndrome patients: pre-diagnosis n=10,414 n (%) | Sjögren's syndrome patients:post-diagnosis n=10,414 n (%) |
|---|---|---|
| Cardiovascular disease | 771 (7.4) | 886 (8.5) |
| Coronary atherosclerosis | 639 (6.1) | 727 (7.0) |
| Cerebrovascular disease | 653 (6.3) | 711 (6.8) |
| MACE Component Score | 392 (3.8) | 482 (4.6) |
| Transient Ischaemic Attack / stroke | 297 (2.9) | 328 (3.1) |
| Angina pectoris | 178 (1.7) | 186 (1.8) |
| Myocardial infarction | 74 (0.7) | 133 (1.3) |
| Unstable angina | 75 (0.7) | 103 (1.0) |
| Percutaneous coronary intervention | 30 (0.3) | 49 (0.5) |
| Coronary artery bypass Graft | 15 (0.1) | 23 (0.2) |
| Cardiovascular death | 0 | 0 |

MACE: major cardiovascular event.

**Table VI.** Medication prescriptions in the 12-month post-diagnosis of Sjögren's syndrome.

| Medication category | Total Sjögren's syndrome patients n=10,414 n (%) | Sjögren's syndrome patients, with other autoimmune conditions n=5,610 n (%) | Sjögren's syndrome patients, without other autoimmune conditions n=4,804 n (%) | Patients with *vs*. without other autoimmune conditions *p*-value |
|---|---|---|---|---|
| Eye/mouth medications | 3,356 (32.2%) | 1,775 (31.6%) | 1,581 (32.9%) | **< 0.0001** |
| Synthetic immunosuppressants | 3,344 (32.1%) | 2,476 (44.1%) | 868 (18.1%) | **< 0.0001** |
| Topical steroids | 3,299 (31.7%) | 1,920 (34.2%) | 1,379 (28.7%) | **< 0.0001** |
| Lower-dose steroids | 3,164 (30.4%) | 2,232 (39.8%) | 932 (19.4%) | **< 0.0001** |
| Oral NSAIDs | 3,107 (29.8%) | 1,829 (32.6%) | 1,278 (26.6%) | **< 0.0001** |
| Opioids and other analgesics | 3,014 (28.9%) | 1,856 (33.1%) | 1,158 (24.1%) | **< 0.0001** |
| Neuropathic drugs | 1,932 (18.6%) | 1,222 (21.8%) | 710 (14.8%) | **< 0.0001** |
| Higher-dose steroids | 720 (6.9%) | 448 (8.0%) | 272 (5.7%) | **< 0.0001** |
| Biologics (TNF inhibitors) | 466 (4.5%) | 462 (8.2%) | 4 (0.1%) | < **0.0001** |
| Corticosteroid or NSAID ophthalmic medications | 417 (4.0%) | 226 (4.0%) | 191 (4.0%) | 0.0541 |
| Biologics (non-TNF inhibitors) | 138 (1.3%) | 127 (2.3%) | 11 (0.2%) | < **0.0001** |
| Calcineurin inhibitors | 63 (0.6%) | 48 (0.9%) | 15 (0.3%)) | < **0.0001** |

NSAID: non-steroidal anti-inflammatory drug; TNF: tumour necrosis factor.

*Prescription medications in the post-index period*

Medication use was evaluated using specific drug categories of interest (Table VI); relevant prescriptions for each category were identified in the database (Table VII). In the total SS population, the most frequently prescribed drug categories during the post-index period were eye/mouth medications (32.2%), synthetic immunosuppressants (32.1%), topical steroids (31.7%), and lower-dose steroids (30.4%). Biologic therapies were prescribed for a minority of patients (Table VI).

As approximately 50% of SS patients had a concurrent autoimmune diagnosis, we compared their prescriptions to those of SS patients without other autoimmune diagnoses (n=4,804). When comparing these 2 SS subsets, eye/mouth medications were prescribed significantly more frequently to patients without other autoimmune conditions, while all other medication classes (other than ophthalmic) were prescribed significantly less frequently to patients without other autoimmune conditions ($p$<0.001) (Table VI).

In the total SS population (with and without other autoimmune conditions), the most frequently prescribed initial medications of interest after SS diagnosis were eye/mouth medications (15.6%), synthetic immunosuppressants (14.5%), and oral NSAIDs (13.1%) (Table VIII). Only 2% of patients were prescribed biologic therapies (TNF or non-TNF inhibitors) as the first medication category of interest after diagnosis of SS, while 15.1% of the total SS population was not prescribed any of the therapies of interest over the entire 1-year post-index period.

*Prescription changes pre- to post-index*

When comparing the use of drugs of interest before and after the index date

**Table VII.** Medication categories of interest and prescriptions associated with the treatment of Sjögren's syndrome.

| Medication category | Prescribed drugs identified in the claims database (in alphabetical order) |
|---|---|
| Eye/Mouth medications* | Cevimeline, cyclosporine ophthalmic, pilocarpine, triamcinolone oral |
| Corticosteroid or NSAID Ophthalmic medications | Dexamethasone, diclofenac, ketorolac, prednisolone |
| Lower-dose steroids, oral or parenteral (≤20mg prednisone/day or equivalent) | Dexamethasone ≤3mg, hydrocortisone ≤80mg, methylprednisolone ≤16mg, prednisolone ≤20mg, prednisone ≤20mg |
| Higher-dose steroids, oral or parenteral (>20 mg prednisone/day or equivalent) | Dexamethasone >3mg, methylprednisolone >16mg, prednisolone >20mg, prednisone >20mg |
| Topical steroids (including dermal, nasal or inhalational) | Alclometasone, amcinonide, betamethasone, clobetasol, clocortolone, desonide, desoximetasone, diflorasone, fluocinolone, fluocinonide, flurandrenolide, fluticasone, halcinonide, halobetasol, hydrocortisone, mometasone, triamcinolone |
| Oral NSAIDs | Celecoxib, diclofenac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac |
| Opioids and other analgesics | Butalbital, carisprodol, codeine, hydrocodone, oxycodone, propoxyphene, tramadol |
| Neuropathic drugs | Duloxetine, gabapentin, pregabalin |
| Calcineurin inhibitors | Pimecrolimus, tacrolimus |
| Synthetic immunosuppressants | Azathioprine, chloroquine, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate, thalidomide |
| Biologics: TNF inhibitors | Adalimumab, certolizumab, etanercept, golimumab, infliximab |
| Biologics: non-TNF inhibitors | Abatacept, belimumab, efalizumab, natalizumab, rituximab, tocilizumab, ustekinumab |

NSAID: non-steroidal anti-inflammatory drug; TNF: tumour necrosis factor
*Lubricant eyedrops were not included due to their availability without a prescription.

**Table VIII.** Initial medication category prescribed in the 12 months post-diagnosis of Sjögren's syndrome.

| First category prescribed after diagnosis of Sjögren's syndrome | Total Sjögren's Syndrome Population (n=10,414) n (%) |
|---|---|
| Eye/ mouth medications | 1,622 (15.6) |
| Synthetic immunosuppressants | 1,512 (14.5) |
| NSAIDS | 1,366 (13.1) |
| Topical steroids (including nasal or inhalation application) | 1,096 (10.5) |
| Lower-dose steroids | 1,015 (9.7) |
| Neuropathic drugs | 666 (6.4) |
| Biologics (TNF inhibitors) | 169 (1.6) |
| Higher-dose steroids | 160 (1.5) |
| Corticosteroid or NSAID ophthalmic medications | 134 (1.3) |
| Biologics (non-TNF inhibitors) | 45 (0.4) |
| Calcineurin inhibitors | 9 (0.1) |
| No prescriptions in any of the drug categories of interest | 1,569 (15.1) |

NSAID: non-steroidal anti-inflammatory drug; TNF: tumour necrosis factor.

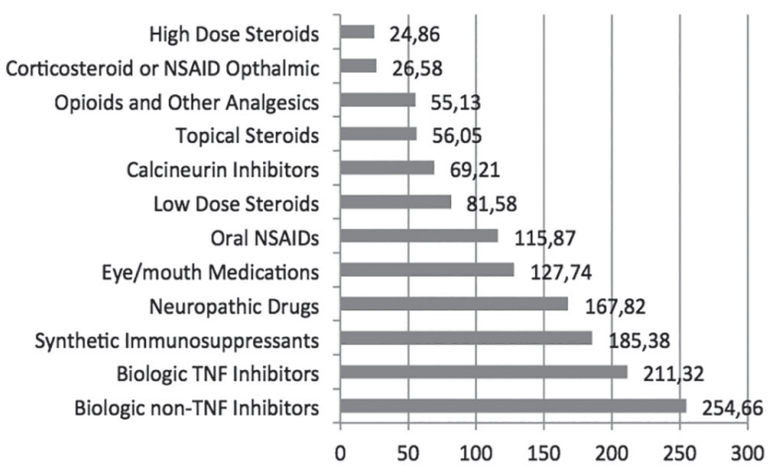


**Fig. 1.** Mean total supply days for medications prescribed to Sjögren's syndrome patients (n=10,414) in the 12 months post-diagnosis.
NSAID: non-steroidal anti-inflammatory drug; TNF: tumour necrosis factor.

in the total SS population, we found that prescriptions for some eye/mouth medications more than doubled *(e.g.* topical cyclosporine [8.4% to 16.4%], cevimeline [5.3% to 14.1%], and pilocarpine [2% to 7.2%], data not shown). Prescriptions for all remaining categories of interest were stable or slightly increased from the pre- to post-index period.

A variety of biologic agents (TNF and non-TNF inhibitors) were prescribed to the total SS population, with etanercept and adalimumab being the most frequent (Table IX). In the subset of SS patients with other autoimmune conditions, we found that the frequency of prescriptions for biologic agents remained stable between the pre- and post-index periods, while synthetic immunosuppressant therapy generally increased (Table IX). In the subset of SS patients without other autoimmune conditions, prescriptions for biologic therapies also remained similar pre- and post-index periods, while prescriptions for synthetic immunosuppressants more than doubled, mostly driven by hydroxychloroquine (2.9% to 15.7%), methotrexate (0.7% to 2%) and azathioprine (0.3% to 1%) (Table IX).

*Medication days of supply*

The total number of days of therapy per prescription during the 1-year post-index period was calculated for each medication and averaged across medication classes. Biologics and synthetic immunosuppressants had the largest number of supply days during the post-index period, while higher-dose steroids, ophthalmic NSAIDs/steroids, and opioids and analgesics had the least (Fig. 1).

*Healthcare resource utilisation and costs*

A variety of healthcare specialists were utilised during the 1-year post-index period, with the most frequent being rheumatology (52.2%), family practice (48.7%), internal medicine (46.8%), and obstetrics and gynaecology (30.9%). Ten percent or more saw dermatologists, ophthalmologists, otolaryngologists, or gastroenterologists (Table X).

All-cause healthcare resource utilisation significantly increased post-index for both outpatient medical visits and hospitalisations, resulting in a 20% increase in the mean number of medical visits per person (Table XI).

During the post-index period, almost all (99%) patients had outpatient visits, with an average of 26.9 visits per person. Outpatient visits specifically associated with SS occurred in approximately 95%, with an average of 3.6 visits per year. Approximately 20% had at least 1 hospitalisation, with >25% of these listing the SS diagnosis code as the primary claim (Table XI).

During the 1-year post-index period, all-cause healthcare hospitalisation, outpatient, and ER visit and pharmacy costs averaged $20,416 per person, with outpatient visits accounting for the highest percentage of costs (51%) (Table XII). Almost 11% of the total medical (non-pharmacy) costs ($1,742.2) were Sjögren-related. Overall, there was a statistically significant increase of 40% in all-cause healthcare costs in the year after SS diagnosis, compared to the year before.

## Discussion

In this study, we identified 10, 414 patients newly diagnosed with SS in a large US employer-based claims database The demographics of our SS patient cohort were consistent with published epidemiologic studies, showing a 9:1 female to male predominance, and SS diagnosis in the fourth or fifth decade of life (25). Also consistent

**Table IX.** Immunosuppressant therapies in the pre- and post-index periods in Sjögren's syndrome patients, both with and without other autoimmune conditions.

| | Total Sjögren's Syndrome Patients | | Sjögren's Syndrome Patients, with other autoimmune conditions | | Sjögren's Syndrome Patients, without other autoimmune conditions | |
|---|---|---|---|---|---|---|
| | Pre-diagnosis period n=10,414 n (%) | Post-diagnosis period n=10,414 n (%) | Pre-diagnosis period n=4,631 n (%) | Post-diagnosis period n=5,610 n (%) | Pre-diagnosis period n=5,783 n (%) | Post-diagnosis period n=4,804 n (%) |
| Synthetic immunosuppressants | | | | | | |
| Hydroxychloroquine | 820 (7.9%) | 2,270 (21.8%) | 654 (14.1%) | 1515 (27.0%) | 166 (2.9%) | 755 (15.7%) |
| Methotrexate | 643 (6.2%) | 1,030 (9.9%) | 603 (13.0%) | 932 (16.6%) | 40 (0.7%) | 98 (2.0%) |
| Azathioprine | 139 (1.3%) | 278 (2.7%) | 121 (2.6%) | 229 (4.1%) | 18 (0.3%) | 49 (1.0%) |
| Leflunomide | 117 (1.1%) | 189 (1.8%) | 110 (2.4%) | 180 (3.2%) | 7 (0.1%) | 9 (0.2%) |
| Mycophenolate | 40 (0.4%) | 137 (1.3%) | 37 (0.8%) | 121 (2.2%) | 3 (0.05%) | 16 (0.3%) |
| Cyclophosphamide | 31 (0.3%) | 57 (0.5%) | 23 (0.5%) | 46 (0.8%) | 8 (0.1%) | 11 (0.2%) |
| Chloroquine | 16 (0.2%) | 24 (0.2%) | 14 (0.3%) | 21 (0.4%) | 2 (0.03%) | 3 (0.1%) |
| Cyclosporine | 6 (0.1%) | 3 (0.03%) | 3 (0.06%) | 3 (0.05%) | 3 (0.05%) | 0 |
| Biologics: TNF inhibitors | | | | | | |
| Etanercept | 180 (1.7%) | 214 (2.1%) | 174 (3.8%) | 211 (3.7%) | 6 (0.1%) | 3 (0.1%) |
| Adalimumab | 146 (1.4%) | 177 (1.7%) | 143 (3.1%) | 176 (3.1%) | 3 (0.1%) | 1 (0.02%) |
| Infliximab | 67 (0.6%) | 86 (0.8%) | 67 (1.4%) | 86 (1.5%) | 0 | 0 |
| Certolizumab | 8 (0.1%) | 22 (0.2%) | 8 (0.2%) | 22 (0.4%) | 0 | 0 |
| Golimumab | 11 (0.1%) | 18 (0.2%) | 11 (0.2%) | 18 (0.3%) | 0 | 0 |
| Biologics: non-TNF inhibitors | | | | | | |
| Abatacept | 43 (0.4%) | 60 (0.6%) | 43 (0.9%) | 60 (1.1%) | 0 | 0 |
| Rituximab | 38 (0.4%) | 63 (0.6%) | 33 (0.7%) | 52 (0.9%) | 5 (0.1%) | 11 (0.2%) |
| Tocilizumab | 3 (0.03%) | 12 (0.1%) | 3 (0.06%) | 12 (0.2%) | 0 | |
| Natalizumab | 2 (0.02%) | 1 (0.009%) | 2 (0.04%) | 1 (0.02%) | 0 | 0 |
| Ustekinumab | 1 (0.009%) | 0 | 1 (0.02%) | 0 | 0 | 0 |
| Belimumab | 0 | 5 (0.05%) | 0 | 5 (0.09%) | 0 | 0 |
| Efalizumab | 0 | 1 (0.009%) | 0 | 1 (0.02%) | 0 | 0 |

TNF: tumour necrosis factor.

with the literature, approximately 50% of the patients in our study were diagnosed with another concurrent autoimmune disease, with RA and SLE being the most prevalent. Other commonly occurring medical conditions were typical of this patient demographic and included hypertension, osteoarthritis, and hyperlipidaemia.

Elevated CV risk factors and increased rates of MI and cerebrovascular accident (CVA) in SS have been recently highlighted (26-31). In our cohort, CV risk factors present during the 1-year period after SS diagnosis included: hypertension (37.6%), hyperlipidaemia (30.3%), and diabetes (11.4%). Significantly, the number of SS patients with medical claims for MI nearly doubled (0.7% to 1.3%) from the 1-year pre- to the 1-year post-SS diagnosis, as did the number of patients with claims for CABG (0.1% to 0.2%), while the number of patients with medical claims for TIA/stroke increased approximately 15% (2.9% to 3.1%). These findings are consistent with published reports in this patient population (29-31). In a prospective study of SS registry patients in the UK, Juarez and colleagues found that 50% had hypertension, and were 2 times more likely to have this diagnosis compared to age- and sex-matched controls (29). Bartoloni and colleagues retrospectively analysed a cohort of pSS female patients regularly attending 5 Italian rheumatology centers and compared them to an age-matched, healthy control female popu-

**Table X.** Healthcare providers visited in the 12 months post-diagnosis of Sjögren's syndrome.

| Healthcare Provider Utilisation | Sjögren's Syndrome Patients: post-diagnosis n=10,414 n (%) |
|---|---|
| Rheumatologist | 5,441 (52.2) |
| Family practice | 5,068 (48.7) |
| Internal medicine | 4,875 (46.8) |
| Obstetrics and gynaecology | 3,213 (30.9) |
| Dermatology | 2,365 (22.7) |
| Ophthalmology | 2,000 (19.2) |
| Otolaryngology | 1,958 (18.8) |
| Gastroenterology | 1,565 (15.0) |
| Cardiovascular/cardiology | 1,442 (13.8) |
| Neurology | 1,317 (12.6) |
| Medical doctor, not elsewhere classified | 1,235 (11.9) |
| Urology | 734 (7.0) |
| Allergy and immunology | 493 (4.7) |
| Oncology | 434 (4.2) |
| Dental specialist | 132 (1.3) |
| Psychiatry | 104 (1.0) |
| Dentist | 55 (0.5) |

**Table XI.** Healthcare resources utilised during the 12-month pre-diagnosis *versus* the 12-month post-diagnosis of Sjögren's syndrome.

| Sjögren's Syndrome Patients, Healthcare Resource Utilisation | | | | | |
|---|---|---|---|---|---|
| | n=10,414 | | | | |
| | Pre-diagnosis, all causes n=10,414 | | Post-diagnosis, all causes n=10,414 | | *p*-value pre-diagnosis *vs.* post-diagnosis |
| | n (%) | Mean event per person (± SD) | n (%) | Mean event per person (± SD) | |
| Healthcare Resource Utilisation, all Outpatient visits | 10,342 (99.3%) | 22.5 (18.7) | 10,408 (99.9%) | 26.9 (20.3) | <0.0001 |
| Emergency Department visits | 3,078 (29.6%) | 0.6 (1.8) | 3,187 (30.6%) | 0.6 (1.5) | = 0.055 |
| Hospitalisations | 1,240 (11.9%) | 0.7 (4.3) | 2,029 (19.5%) | 1.3 (5.3) | <0.0001 |
| Total Medical visits | 10,347 (99.4%) | 23.8 (20.9) | 10,414 (100%) | 28.8 (23.4) | <0.0001 |
| Healthcare Resource Utilisation, associated with ICD Code 710.2[#] | | | | | |
| Outpatient visits | | | 9,857 (94.6) | 3.6 (2.7) | |
| Emergency Department visits | | | 302 (2.9) | 0 | |
| Hospitalisations | | | 525 (5.04) | 0.1 (0.7) | |
| Total Medical visits | | | 10,101 (96.9) | 3.8 (2.8) | |

SD: standard deviation of the mean. [#]Patients were newly diagnosed with SS (by definition, those with no SS medical claims during the pre-index period), thus, there are no SS associated healthcare costs in the pre-index period.

**Table XII.** Healthcare costs accrued during the 12-month pre-diagnosis *versus* the 12 months post-diagnosis of Sjögren's syndrome.

| Sjögren's Syndrome Patients | | | | | |
|---|---|---|---|---|---|
| | n= 10,414 | | | | |
| | Pre-diagnosis | | Post-diagnosis | | mean cost pre-diagnosis *vs.* post-diagnosis *p*-value |
| | n (%) | Mean cost per person (± SD) median | n (%) | Mean cost per person (± SD) median | |
| Healthcare costs, all Outpatient visits | 10,342 (99.3) | $8,060.2 (15,611.9) 4,119.5 | 10,408 (99.9) | $10,378 (23,419.4) 5,140.8 | <0.0001 |
| Emergency Department visits | 3,078 (29.6) | $405.3 (1,500.5) 0 | 3,187 (30.6) | $477.9 (1,839.6) 0 | <0.0001 |
| Hospitalisations | 1,240 (11.91) | $2,947.3 (20,444.2) 0 | 2,029 (19.5) | $5,393.8 (25,719.5) 0 | <0.0001 |
| Total Medical visits | 10,347 (99.4) | $14,612.1 (29,913.7) 7,320.2 | 10,414 (100) | $20,416.5 (41,117.3) 9,595.5 | <0.0001 |
| Pharmacy[*] | 9,624 (92.5) | $3,199.3 (6,185.7) 1514.3 | 9,694 (93.1) | $4,166.8 (7,778.4) 2,127.7 | <0.0001 |
| Healthcare Costs, associated with ICD Code 710.2[#] Outpatient visits | | | 9,857 (94.6) | $1,259.5 (7277.5) 432.2 | |
| Emergency Department visits | | | 302 (2.9) | $24 (226.2) 0 | |
| Hospitalisations | | | 525 (5.04) | $458.9 (3745.4) 0 | |
| Total Medical visits | | | 10,101 (96.9) | $1,742.4 (8275.3) 461.9 | |

[*]Outpatient prescription drug claims do not have corresponding diagnosis codes, thus cannot be associated with Sjögren's syndrome (ICD-9 code 710.2). [#]Patients were newly diagnosed with SS (by definition, those with no SS medical claims during the pre-index period), thus, there are no SS associated healthcare costs in the pre-index period.

lation. The pSS patients had higher rates of cerebrovascular events (2.5% *vs*. 1.4%, *p*=0.005) and MI (1.0% *vs*. 0.4%, *p*=0.002) compared to the control group (30). Additionally, in a population-based study of SS patients (31), the rate of MI and CVA were 2.4% and 1.6%, respectively, during 3 years of follow-up *versus* 1.2% and 1.1%, respectively, in matched controls. Therefore, the authors concluded that the risk of MI was approximately 2.4 times higher in SS patients, and the risk of CVA was 1.6 times higher. Moreover, the authors found that in the first year

after SS diagnosis, the risk of MI was 3.6 times higher than in controls. Together with our findings, these data underscore the need for CV risk stratification and management in SS, especially at the time of initial diagnosis.

The variety of disease manifestations in SS patients, coupled with a lack of approved disease-modifying therapies, necessitates a multipronged pharmacologic approach, which may include corticosteroids, anti-inflammatory medications, synthetic immunosuppressants, and biologic agents.

Nearly 85% of the SS patients in our study were prescribed some category of SS-related medication, however, despite the wide range of drugs examined, 15.1% of patients in our study were not prescribed any of the potential Sjögren's therapies after diagnosis. Although this may have been due to lower SS disease activity or other severe medical conditions in some of these patients, this finding supports the idea that there is a lack of effective treatment options for patients newly diagnosed with SS.

For patients receiving Sjögren-related therapies, we observed that pharmacologic management was consistent with published data (18, 19), SS patients without other autoimmune conditions were most often prescribed eye/mouth medications, while the medication category most commonly prescribed to SS patients with concurrent autoimmune conditions was synthetic immunosuppressants, suggesting that these medications were not prescribed specifically for SS. The most frequently prescribed initial therapy category for all SS patients after diagnosis was eye/mouth medications, which underscores the predominance of sicca symptoms in this population, as well as the fact that no synthetic or biologic DMARDs (bDMARDs) have yet been approved for the treatment of SS.

To date, the formal investigation of bDMARDs in SS has been limited, with only 15 clinical trials in 20 years (1994 to 2014) (329). In our study, biologic therapies were prescribed to a small percentage of SS patients, with only 4.5% prescribed TNF inhibitors and 1.3% prescribed non-TNF inhibitors. These numbers fell to 0.1% and 0.2%, respectively, in SS patients without other autoimmune conditions, supporting the idea that bDMARDs are not being utilised specifically for the treatment of SS. These real-world practices are consistent with data from 3 randomised, controlled trials published in 2004 (before the observation period of this study), which demonstrated the ineffectiveness of TNF-inhibitors in SS (20-22). In our study, bDMARD use remained low post-SS diagnosis, but rituximab was the most frequently prescribed biologic in SS patients without other autoimmune conditions, perhaps due to data suggesting that B-cell-targeted therapies show some promise in SS (33, 34). The low frequency of biologic prescriptions in SS stands in marked contrast to bDMARD use in patients with RA; in a US registry study (2002–2006) of patients with established RA approximately 40% were prescribed bDMARD (35)

Not unexpectedly, we observed that the mean duration of prescribed treatment was shorter for more toxic drugs, *i.e.* high-dose steroids, 25 days/year and longer for systemic immunomodulators, *i.e.* synthetic immunosuppressants, 185 days/year and bDMARDs, 255 days/year).

Physician specialists seen by SS patients in our study represented a diverse group of practitioners, underscoring the multidisciplinary approach required by this disease. The largest healthcare burden during the 1-year post-index period stemmed from the outpatient visits required by nearly 100% of SS patients to various providers, averaging nearly 4 visits per patient in a 1-year period.

Our study is the largest retrospective observational study (10,414 patients) to highlight the economic impact of SS in the US. We found a high healthcare impact associated with SS, similar to data reported for SS in the UK (15). Interestingly, compared with the year pre-diagnosis, all-cause healthcare costs were 40% higher post-SS diagnosis. The high cost of managing SS is pronounced even when compared with the healthcare burden of RA. In the Medical Expenditure Panel Survey of 2008, the mean annual total cost per RA patient was ~$13,000/year (measured in 2008 dollars), which is lower than the cost we identified for SS ($20,417/year) (36). Given the heterogenous clinical manifestations of SS, the full economic burden of the disease should be considered from both ends of the disease spectrum, including local *vs.* systemic disease and more complicated sequelae such as lymphoma; such an evaluation, not currently available in the literature, would add to the understanding of the societal impact of SS.

Limitations of our analyses include those inherent to claims database studies such as the retrospective nature, a lack of availability of clinical details and accuracy of diagnosis precluding the ability to ascertain the disease severity of SS or what classification criteria were used to diagnose the disease, and details of the other medical conditions in these patients. While the datasets used encompass a large, nationally representative sample of Americans with employer and Medicare-provided health insurance, individuals with private insurance alone, Medicaid, or the uninsured are not represented. As medication treatment patterns were assessed using prescription fill data, additional information, such as prescription adherence rates, and the specific indication for each prescription, were not available. Similarly, utilisation and costs of over-the-counter medications could not be assessed. In this regard, the SSF estimates that SS patients spend an additional $2,000 to $4,700 per year on medically necessary over-the-counter products (37). Although direct medical costs of third-party payers were analysed, other economic implications of SS, such as absence from work or school, loss of productivity, costs of disability and family impact were not available.

This study is the first to characterise a large cohort of real-world patients with SS from a US claims database. Our findings are consistent with previous reports that indicate this patient population is burdened by a variety of concurrent autoimmune and metabolic diseases. In alignment with recent reports of elevated CV risk in SS patients', our study revealed an increased number of patients with CV claims in the first

year after SS diagnosis. With respect to pharmacotherapy, we observed that although most patients were prescribed 1 or more drugs likely to impact SS, these drugs were more frequently prescribed to patients who also had another concurrent autoimmune disease, and 15% did not receive any of these prescriptions. In those who did, pharmacologic management consisted primarily of lower-potency immunomodulators and symptomatic treatments, supporting the idea that treatment options for SS are limited. This study is also the first to identify and analyse the significantly increased healthcare costs associated with SS in the US, an aspect that is currently underrepresented in the literature.

**Acknowledgements**

We would like to acknowledge Yali Wang and Chen-Yen Lin for their statistical input into study design and data analyses.

## References

1. PATEL R, SHAHANE A: The epidemiology of Sjögren's Syndrome. *Clin Epidemiol* 2014; 6: 247-55.
2. HALL SA, JUNEJA M, VINIKOOR L, MUSSELLI C, FRANCHIMONT N: The prevalence of Sjögrens's Syndrome in United States health insurance claims. *Pharmacoepid Drug Saf* 2015; 24: 371-72.
3. SHIBOSKI SC, SHIBOSKI CH, CRISWELL LA *et al*.: American College of Rheumatology Classification Criteria for Sjögren's Syndrome: A Data-Driven, Expert Consensus Approach in the SICCA Cohort. *Arth Care Res* 2012; 64: 475-87.
4. http://info.sjogrens.org/conquering-sjogrens/bid/359061/Ask-the-SSF-Staff-Treating-Primary-vs-Secondary-Sjögren-s. Accessed January 26, 2016.
5. FOX PC: Autoimmune diseases and Sjögren's Syndrome. An autoimmune exocrinopathy. *Ann NY Acad Sci* 2007; 1098: 15-21.
6. GARCIA-CARRASCO M, RAMOS-CASALS M, ROSAS J *et al*.: Primary Sjögren's Syndrome. Clinical and immunologic disease patterns in a cohort of 400 patients. *Medicine* 2002; 81: 270-80.
7. RAMOS-CASALS M, BRITO-ZERON P, BOADA AB, SISO-ALMIRALL A: Sjögren's Syndrome: beyond sicca involvement. *Autoimmune Dis* 2011. DOI: 10.1007/978-0-85729-358-9_5.
8. SEROR R, BOOTSMA H, BOWMAN SJ *et al*.: Outcome measures for primary Sjögren's syndrome. *J Autoimmun* 2012; 39: 97-102.
9. TINCANI A, ANDREOLI L, CAVAZZANA I *et al*.: Novel aspects of Sjögren's syndrome in 2012. *BMC Medicine* 2013; 11: 93-109.
10. SEROR R, GOTTENBERG JE, DEVAUCHELLE-PENSEC V *et al*.: European League Against Rheumatism Sjögren's Syndrome Disease Activity Index and European League Against Rheumatism Sjögren's Syndrome Patient-Reported Index: A Complete Picture of Primary Sjögren's Syndrome Patients. *Arthritis Care Res* 2013; 65: 1358-64.
11. RAMOS-CASALS M, BRITO-ZERÒN P, SISÒ-ALMIRALL A, BOSCH X: Primary Sjögren syndrome. *BMJ* 2012, 344:e3821
12. SUTCLIFFE N, STOLL T, PYKE S, ISENBERG DA: Functional disability and end organ damage in patients with Systemic Lupus Erythematosus (SLE), SLE and Sjögren's Syndrome, and Primary SS. *J Rheumatol* 1998; 25: 63-8.
13. STROMBECK B, EKDAHL C, MANTHORPE R, WIKSTROM I, JACOBSSON L: Health related quality of life in primary Sjögren's Syndrome, rheumatoid arthritis, and fibromyalgia compared to normal population data using the SF36. *Scand J Rheumatol* 2000; 29: 20-8.
14. SEGAL B, BOWMAN SJ, FOX PC *et al*.: Primary Sjögren's Syndrome: health experiences and predictors of health quality among patients in the United States. *Health Qual Life Outcomes* 2009; 7: 46.
15. CALLAGHAN R, PRABU A, ALLAN RB *et al*.: Direct healthcare costs and predictors of cost in patients with Primary Sjögren's Syndrome. *Rheumatology* 2007; 46: 105-11.
16. BOWMAN SJ, ST PIERRE Y, SUTCLIFFE N *et al*.: Estimating indirect costs in primary Sjögren's Syndrome. *J Rheumatol* 2010; 37: 1010-5.
17. GOTTENBERG JE, RAVAUD P, PEUCHAL X *et al*.: Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren's Syndrome: The JOQUER randomized clinical trial. *JAMA* 2014; 312: 249-58.
18. RAMOS-CASALS M, BRITO-ZERON P, SISO-ALMIRALL A, BOSCH X, TZIOUFAS AG: Topical and systemic medications for the treatment of primary Sjögren's syndrome. *Nat Rev Rheumatol* 2012; 8: 399-411.
19. BOWMAN S, BARONE F: Biologic treatments in Sjögren's syndrome. *Presse Med* 2012; 41: e495-e509.
20. MARIETTE X, RAVAUD P, STEINFELD S *et al*.: Inefficacy of infliximab in primary Sjögren's Syndrome. Results of the randomized, controlled trial of Remicade in primary Sjögren's Syndrome (TRIPSS). *Arthritis Rheum* 2004; 50: 1270-74.
21. SANKAR V, BRENNAN MT, KOK MR *et al*.: Etanercept in Sjögren's Syndrome. A twelve week randomized, double-blind, placebo-controlled pilot clinical trial. *Arthritis Rheum* 2004; 50: 2240-5.
22. ZANDBELT MM, DE WILDE P, VAN DAMME P *et al*.: Etanercept in the treatment of patients with primary Sjögren's Syndrome: A pilot study. *J Rheum* 2004; 31: 96-101.
23. http://truvenhealth.com/your-healthcare-focus/life-sciences/marketscan-databases-and-online-tools. Accessed January 26, 2016.
24. BERNATSKY S, LINEHAN T, HANLY JG: The accuracy of administrative data diagnoses of systemic autoimmune rheumatic diseases. *J Rheumatol* 2011; 38: 1612-16.
25. MAVRAGANI CP, MOUTSOPOULOS HM: The geoepidemiology of Sjögren's Syndrome. *Autoimmun Rev* 2010; 9: A305-A310.
26. GRAVANI F, PAPADAKI I, ANTYPE A *et al*.: Subclinical atherosclerosis and impaired bone health in patients with primary Sjögren's syndrome: prevalence, clinical and laboratory associations. *Arthritis Res Ther* 2015; 17: 99.
27. FERRO F, VAGELLI R, BRUNI C *et al*.: One year in review 2016: Sjögren's syndrome. *Clin Exp Rheumatol* 2016; 34: 161-71.
28. VALIM V, GERDTS E, JONSSON R *et al*.: Atherosclerosis in Sjögren's syndrome: evidence, possible mechanisms and knowledge gaps. *Clin Exp Rheumatol* 2016; 34: 133-42.
29. JUAREZ M, TOMS TE, DEPABLO P *et al*.: Cardiovascular risk factors in women with primary Sjögren's Syndrome: United Kingdom Primary Sjögren's Syndrome Registry results. *Arthritis Care Res* 2014; 66: 757-64.
30. BARTOLONI E, BALDINI C, SCHILLACI G *et al*.: Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study. *J Intern Med*. 2015; 278: 185-92.
31. AVINA-ZUBIETA JA: Increased cardiovascular risk in Sjögren's Syndrome. European League against Rheumatism, 2014 Annual Meeting, Paris, France.
32. SADA PR, ISENBERG D, CIURTIN C: Biologic treatment in Sjögren's Syndrome. *Rheumatology* 2015; 54: 219-30.
33. CARUBBI F, ALUNNO A, CIPRIANI P *et al*.: Rituximab in primary Sjögren's Syndrome: a ten-year journey. *Lupus* 2014; 23: 1337-49.
34. DEVAUCHELLE-PENSEC V, MARIETTE X, JOUSSE-JOULIN S *et al*.: Treatment of primary Sjögren's Syndrome with rituximab: a randomized trial. *Ann Intern Med* 2014; 160: 233-42.
35. LEE SJ, CHANG H, YAZICI Y, GREENBERG JD, KREMER JM, KAVANAUGH A: Utilization trends of tumor necrosis factor inhibitors among patients with rheumatoid arthritis in a United States observational cohort study. *J Rheumatol* 2009; 36: 1611-7.
36. KAWATKAR AA, JACOBSEN SJ, LEVY GD, MEDHEKAR SS, VENKATASUBRAMANIAM KV, HERRINTON LJ: Direct medical expenditure associated with rheumatoid arthritis in a nationally representative sample from the Medical Expenditure Panel Survey. *Arthritis Care Res* 2012; 64: 1649-56.
37. SJÖGREN'S SYNDROME FOUNDATION: Written Testimony from Steven Taylor, Sjögren's Syndrome Foundation CEO House Ways and Means Oversight Subcommittee Hearing: "The Impact of Limitations on the Use of Tax-Advantaged Accounts for the Purchase of Over-the-Counter Medication" April 25, 2012.