LUPUS AROUND THE WORLD

Drugs used in incident systemic lupus erythematosus – results from the Finnish nationwide register 2000–2007

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The objectives of the study were to examine the initial, first-year anti-rheumatic outpatient therapy in patients with incident SLE, as well as the concomitant use of drugs for certain comorbidities, compared to the use in the general population. The Finnish nationwide register data on special reimbursements for medication costs was screened to identify the inception cohort of 566 adult SLE patients (87% females, mean age 46.5 ± 15.9 years) over the years 2000–2007. The patients were linked to the national Drug Purchase Register. Of those, 90% had purchased at least once some disease-modifying anti-rheumatic drugs (DMARDs) during the first year. Hydroxychloroquine was the most common (76%), followed by azathioprine (15%) and methotrexate (13%). With the exception of increase in mycophenolate mofetil, the proportions remained stable over the whole study period 2000–2007. Drugs for cardiovascular diseases, dyslipidemia, diabetes mellitus, hypothyroidism and obstructive pulmonary disease were more frequently purchased than in the sex- and age-adjusted population, with rate ratios ranging from 1.6 to 7.8. Over the years 2000–2007, almost all the patients with incident SLE in Finland started with a DMARD. Higher percentages of SLE patients were on medication for several common chronic diseases than in the population as a whole. Lupus (2016) 25, 666–670.

Key words: Systemic lupus erythematosus; medication; drug; register

Introduction

Systemic lupus erythematosus (SLE) is a multifaceted, challenging autoimmune disease with an unknown etiology and without cure. Current treatment options include antimalarial drugs (AMs), glucocorticoids, with increasing dose according to the severity of the disease and immunosuppressive drugs like azathioprine, mycophenolate mofetil, methotrexate and cyclophosphamide for non-responsive and glucocorticoid-dependent patients.1

Awareness of the need to prevent and treat disease flares and comorbidities in SLE is growing, while the traditional therapy fails to fulfill patient’s needs.2 Although data on comorbidities is incomplete, it is obvious that certain comorbidities add risk to unfavourable outcomes, and must be taken into account while treating SLE patients.1 Metabolic syndrome is common, even in early SLE,3 and the risk of cardiovascular diseases (CVDs) is estimated to be at least two times higher in SLE patients than in the population as a whole. Both traditional risk factors and risks related to SLE itself, especially disease activity and the use of glucocorticoids, have been associated with SLE-related CVDs.4

The purpose of this nationwide register study was to explore the initial anti-rheumatic medication and the use of drugs for certain comorbidities, in incident SLE patients compared to the general Finnish population.

Material and methods

Finland had a total population of 5,300,484 residents at the end of 2007. Residents are over 98% Caucasian.7 All permanent residents are covered by the National Health Insurance which offers...
reimbursement (42%) for the drug costs prescribed by a physician. For drugs used in the treatment of certain chronic diseases like SLE, patients are entitled to a special reimbursement (72% or 100%) if certain clinically defined objective criteria of the disease are fulfilled. For the entitlement a patient must file a medical certificate from a specialist (rheumatologist, internist, nephrologist, or dermatologist) treating SLE, based on appropriate diagnostic examination and including a drug treatment strategy according to good clinical practice. The medical certificate is re-evaluated and approved by an examiner physician at the regional office of the Social Insurance Institution (SII). The administrative process takes usually a couple of weeks. After the reimbursement decision, a respective code is added to the personal health insurance card. If the code is missing, pharmacists actively encourage patients to apply for this benefit while transacting in pharmacies. The special reimbursement decisions are gathered in a nationwide register. All purchases of the reimbursed drugs are recorded in detail (Anatomical Therapeutic Chemical (ATC) – code, amount, date) in a Drug Purchase Register maintained by the SII. The drugs used in outpatient therapy are reimbursed, but not those given in hospitals, which are, therefore, not included in this study.

Patient cohort

Register data on special reimbursement decisions for SLE medication costs was screened to identify – by the international classification of disease code (ICD-10) of SLE (M32) – all incident SLE patients aged 17 years or older between 1 January 2000 and 31 December 2007. The date of the decision was defined as the index day. In addition, the data included sex and date of birth. Any clinical data, or the fulfilment of the American College of Rheumatology (ACR, revised 1997) criteria, was not available.

The patients were linked to the Drug Purchase Register, and data on the anti-rheumatic drugs purchased during the first year after the index day or 31 days before the index day (to cover duration of the administrative handling) were collected. The patient was defined to be on drug therapy if the drug had been purchased at least once during the observation year. The patients were divided in four groups according to index date (2000–2001, 2002–2003, 2004–2005 and 2006–2007). The information on the purchases of glucocorticoids was not available for the years 2006–2007, since prednisolone 5 mg was not reimbursed at that time.

The purchases of drugs for cardiovascular diseases, dyslipidemia, diabetes mellitus, hypothyroidism and obstructive pulmonary disease were collected during the first year after the index day. The drug proportions of incident SLE patients were compared to calculated average annual medication per patient-year in the general population during the observation time, for which statistics are also maintained by the SII. Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) were left out of this calculation, since some of them are sold over-the-counter with no reimbursement.

The data permit was received from the SII (32/26/2007). Patients were analysed anonymously. No approval by the ethics committee was required.

Statistical methods

Statistical significance for the hypotheses of periodic linearity was evaluated by using a generalized linear model with a logit link and a binomial distribution. The probability of medical treatment was calculated on the basis of sex-, age- and calendar-period-specific rates in the general Finnish population. Crude and standardized estimates of the rate ratios (RR) of the drug users were calculated by using Poisson regression models or negative binomial regression models when appropriate.

Results

The incident cohort of 566 adult patients included 492 females and 74 males with mean age 45.7 ± 15.8 and 51.8 ± 15.2 years, respectively. Table 1 shows the number of SLE patients purchasing anti-rheumatic drugs during the first year in two-year calendar periods. A total of 507 (89.6%) patients had purchased DMARDs at least once, whereas only 28 (4.9%) patients were without any anti-rheumatic medication. Over the observation period the proportions of drugs remained almost the same. Hydroxychloroquine (HCQ) was the most frequently purchased DMARD, with the proportions varying between 73% and 80%. This was followed by azathioprine (10%–19%) and methotrexate (9%–17%). Only mycophenolate mofetil became significantly more common, while no oral cyclophosphamide was purchased during the first year from 2004. The proportions of oral glucocorticoids in the initial therapy were at the same level (66%–70%) throughout the periods (2000–2001, 2002–2003 and 2004–2005) available for assessment.
Discussion

In Finland, 90% of the incident patients with SLE had used some DMARDs during the first year. DMARDs are prescribed to almost all incident patients with RA, and rheumatologists are familiar with the use of immunosuppressive drugs. In the present nationwide study, about three quarters purchased AMs. These drugs have been recommended to most of SLE patients, since they are effective in lupus flare prevention, improving long-term survival and decreasing permanent damage accrual, and are beneficial to lipid profile. However, the power of AMs to prevent or treat severe lupus flare is limited.

The most used immunosuppressive agent was azathioprine (15%), and methotrexate was close to that. The use of DMARDs was stable during the period of interest, except for mycophenolate mofetil. Along with the recognition of benefits related to mycophenolate mofetil in SLE, its use has increased in our cohort. Immunosuppressive drugs and AMs help to minimize the dose of glucocorticoids and achieve a balance between their beneficial and harmful effects.

To our knowledge, this is one of the few reports focusing on the medication used in the initial treatment of SLE in a nationwide population. A German study based on the national database of the German Collaborative Arthritis Centres showed an increasing trend in the use of AMs and mycophenolate mofetil and a decreasing trend with glucocorticoids from 1994 to 2012. In 2012 69% of the patients were on glucocorticoids, 56% on AMs, 22% on azathioprine and 15% on mycophenolate mofetil. In the sub-analysis of incident SLE patients, the use of glucocorticoid as initial therapy decreased and the use of NSAIDs increased over time.

Many earlier studies report treatment along with other issues of interest. Those highlighting medicines concentrate mainly on AMs or adherence to medication. Nossent et al. described the first-year drug treatment of SLE among 200 incident patients from 14 European centres over a period of five years ending in 2005. In that cohort, oral glucocorticoids were widely used (83% of patients) and AMs were more infrequent (46%) compared to the present study. In parallel, AMs were prescribed to 48% of 1000 established SLE patients during the 10-year prospective study 1990–2000 in the EURO-lupus cohort, whereas the use of oral steroids decreased significantly over that time. Comparison between studies, however, is impeded by different settings and disease durations; the above-mentioned data were mostly collected from academic referral centres, whereas the present incident cohort was nationwide.
In a community-based observational cohort of established SLE (3095 person-years), Schmajuk et al.\textsuperscript{16} found a 55% patient-informed annual use of HCQ. Over 80\% of the usage was continuous from year-to-year. At least one DMARD was used by 69\% of the patients. Recently, the Spanish cross-sectional RELESSER-T study identified established SLE patients from a multicentre hospital-based registry. Glucocorticoids (89\%) were the most frequently used anti-rheumatic drugs, followed by AMs (83\%), azathioprine (33\%), cyclophosphamide (23\%), methotrexate (17\%) and mycophenolate mofetil (15\%).\textsuperscript{18} An incidence study on SLE patients from the General Practice Research Database in the UK, reported prescriptions of glucocorticoids in over half, AMs in 38\% and azathioprine in 14\% of the patients.\textsuperscript{14} A study on medical costs in SLE reported the use of AMs in 76\%, immunosuppressants in 73\% and glucocorticoids in 93\% of the patients with SLE in active phases of the disease.\textsuperscript{19}

Some evidence suggests that early detection and treatment of SLE leads to favourable prognosis concerning damage accrual and survival.\textsuperscript{20} Disease activity definitions and treatment goals are matters under discussion.\textsuperscript{21} Little is known about how often a prescribed medicine is actually taken in practice.\textsuperscript{22-24} although there are several ways to follow adherence to medication.\textsuperscript{15,25} Low serum concentrations of HCQ are associated with disease flares in SLE.\textsuperscript{17} Previous studies have been based on medication data obtained from questionnaires or medical records,\textsuperscript{14-16,22} whereas ours were collected from the registries. Our data based on medicine purchases probably reflects the real use better than data from prescribed medications, in which primary noncompliance is not taken into account.\textsuperscript{26}

SLE patients carry an excess risk for accelerated atherosclerosis and cardiovascular events (CVEs), which is not explained by the traditional Framingham risk factors such as hypertension, diabetes, hypercholesterolemia and smoking alone. This seems to be disease-related and includes factors like positive anti-phospholipid antibodies, current use of glucocorticoids, renal disease, disease duration and activity.\textsuperscript{4,27,28} The guidelines to prevent and treat hypertension, diabetes and hypercholesterolemia in SLE are adapted from studies conducted in the general population.\textsuperscript{29} In hypertension the first-line drugs are angiotensin converting enzyme (ACE) inhibitors, whereas thiazide diuretics, calcium-channel blockers and beta-blockers are second-line.\textsuperscript{28,29} This recommendation is also reflected in our findings. The use of antihypertensives was more frequent than in age- and sex-adjusted controls.

Glucocorticoids may induce diabetes,\textsuperscript{10} but in the present study exposure to glucocorticoids was of short duration. In diabetes, the treatment among SLE patients is similar to the normal regimen.\textsuperscript{28,29} The medication for diabetes was used a little more often in our incident SLE cohort than in the population.

Data on any favourable impact of statins in SLE is controversial. Atorvastatin failed in prevention of disease activity and atherosclerotic outcomes in a randomized two-year follow-up study.\textsuperscript{30} Statins are still considered beneficial in lowering lipid levels in SLE patients, since in the general population the preventive effect is well-documented, and hypercholesterolemia plays an important role as a cause of CVEs among SLE patients.\textsuperscript{1,28,29} In the above mentioned RELESSER-T study a quarter of the patients received statins.\textsuperscript{18} In the present study 14\% of SLE patients used lipid lowering therapy (mainly statins), which was 3.5 times more frequent than in the general population.

A comorbidity study on SLE in Puerto Rico detected a high frequency of hypothyroidism among SLE patients, but did not report its prevalence in the general population.\textsuperscript{31} There is also evidence on higher prevalence of symptomatic and subclinical hypothyroidism in SLE patients compared to controls or the general population.\textsuperscript{32,33} In our study the medication for hypothyroidism was almost five times more common than in the general population. SLE patients are generally under tight disease control, with regular outpatient visits. This may lead to earlier diagnosis and treatment of milder comorbidities than in the general population.

The strengths of our study lie in the nationwide coverage and the comparison with the general population, whereas the lack of clinical data and information on fulfilment of the ACR97 classification criteria for SLE are limitations. However, during the first year, 90\% of all patients had purchased DMARDs, which can be taken as an indicator of a clinically-meaningful condition.

In summary, this study shows prevalent use of DMARDs in patients with incident SLE in Finland. Drugs for the treatment or prevention of comorbidities are more common than in the general population.

Declaration of Conflicting Interests

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