ORIGINAL ARTICLE

Title: Fifteen-year nationwide trends in systemic glucocorticoid drug use in Denmark

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ABSTRACT

Objective: Glucocorticoid treatment of inflammatory disorders is associated with significant adverse effects related to glucocorticoid excess as well as adrenal insufficiency. This necessitates awareness of its use. We therefore investigated trends in systemic glucocorticoid use as well as morbidity and comedications among users.

Design: Cross-sectional drug utilization study.

Methods: We conducted a population-based study of 926,314 users of systemic glucocorticoids (oral and injectable formulations) from 1999 to 2014 using Danish nationwide registries. We computed annual prevalence and incidence of systemic glucocorticoid use and prevalence of comedications and morbidity. Further, we assessed annual amount of disease-modifying drug use.

Results: Of the 926,314 users of systemic glucocorticoids, 54% were female and median age at first-time use was 55 years. The annual prevalence was ≈ 3% while the incidence was ≈ 1.4/100 person years (p-y). Both figures remained constant from 1999 to 2014. In the elderly, the annual prevalence was 6.7%-7.7% (60-79 years of age) and 9.7%-11% (≥80 years of age). Incidence increased among persons aged ≥80 from 3.0/100 p-y in 1999 to 3.6/100 p-y in 2014. Concomitantly, the annual amount of e.g. methotrexate, azathioprine and tumor necrosis factor (TNF)-alpha agents increased and new biological agents emerged. The most frequent comedications were antibiotics (49%), cardiovascular drugs (38%), and NSAIDs (37%).

Conclusions: Our findings confirm a widespread use of systemic glucocorticoids, especially in the elderly, which prevails despite increased use of disease-modifying drugs. The continuously prevalent use of glucocorticoid use constitutes a challenge for the endocrine community.

INTRODUCTION

Synthetic glucocorticoids are potent anti-inflammatory drugs introduced into clinical practice in the 1950s to treat rheumatoid arthritis (RA) (1). Since then, glucocorticoids have proven useful in the treatment of numerous conditions, including other rheumatic diseases, asthma, chronic obstructive pulmonary disease (COPD), and inflammatory bowel diseases (2-6). Serious adverse effects, however, are associated with glucocorticoid use, including features of iatrogenic Cushing's syndrome, diabetes (7), and osteoporosis (8). Moreover, glucocorticoid use and discontinuation increases the risk of adrenal insufficiency (9, 10). In addition, studies have reported increased risk of cardiovascular diseases and venous thromboembolism (11-14) as well as neuropsychiatric symptoms and disorders (15). Several studies from western countries have estimated prevalence of glucocorticoid use to range between 0.5% to 17% depending on calendar year, setting and methodology (16-22). Updated and population-based data on glucocorticoid utilization and knowledge on comedication use and morbidity remain important. Therefore, we examined annual prevalence and incidence of systemic glucocorticoid use (oral and injectable formulations) and described prevalence of comedications and morbidity among users.

MATERIALS AND METHODS

Setting

Denmark provides its entire population with tax-supported healthcare, guaranteeing access to primary and secondary care free-of-charge. A unique personal civil registration number is assigned to all Danish residents at birth or upon immigration, enabling accurate and unambiguous individual-level linkage of relevant registries (23).

Systemic glucocorticoids, disease-modifying drugs and comedications

We used the Danish National Prescription Registry to identify all persons in the Danish population who redeemed prescriptions for systemic glucocorticoids (oral and injectable formulations) between 1 January 1999 and 31 December 2014 (24). The Danish National Prescription Registry records information on all prescriptions redeemed in Denmark on an individual level, including the civil registration number of the patient, the medication classification code [Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization], and date of dispensing (24). A limitation of the Danish National Prescription Registry is that medication provided directly by the hospital sector, which includes most disease-modifying drugs for the treatment of the underlying conditions, is not captured. We therefore used Medstat (http://www.medstat.dk/en) to retrieve information on annual amount of conventional disease-modifying drug and biological disease-modifying drug use in the primary health care sector and in the hospital sector. The publicly available Medstat website provides aggregated Medstat statistics that are complete from 1999 onwards and allows for extraction of annual amount used (primary healthcare and hospital sector separately and in a combined total) (25). The amount is expressed in defined daily doses (DDD) developed by WHO and defined as the assumed average maintenance daily dose of a drug used for its main indication in adults.(26) Methotrexate and rituximab are not expressed in DDD but in gram (active substance). Codes for systemic glucocorticoids, disease-modifying drugs, and comedications are provided in Supplementary Table 1 and Supplementary Table 2.

Morbidity

Information on morbidity leading to hospital contacts (hospitalizations and outpatient clinic visits) was obtained from the Danish National Patient Registry (DNPR) (27). The DNPR has captured information on all inpatient stays at Danish public hospitals since 1977 and on all outpatient clinic and emergency room visits at public hospitals since 1995. Data recorded in

the DNPR include the patient's civil registration number, dates of admission and discharge or outpatient visits, and up to 20 discharge diagnoses for each contact, classified according to the Eighth Revision of the International Classification of Diseases (ICD-8) until 1994 and the Tenth Revision (IDC-10) thereafter (27). We assessed patients' history of hospital contacts for pulmonary, cardiovascular, gastrointestinal, endocrine, neurological, rheumatic, renal, and dermatological disease, as well as for cancer (Supplementary Table 3 for ICD codes).

Statistical analyses

We first described systemic glucocorticoid users at the time of initial use, including sex, age, and generic type of systemic glucocorticoid.

Second, we computed annual prevalence and incidence of systemic glucocorticoid users from 1999 to 2014 in the overall population and stratified by sex and age group (0-19, 20-39, 40-59, 60-79, and ≥ 80 years). Annual prevalence was defined as the number of persons who redeemed at least one prescription for a systemic glucocorticoid each year divided by the number of people in the population on January 1st of each year. The incidence was calculated as number of initiators (defined as persons who redeemed a prescription for a systemic glucocorticoid without any preceding prescriptions up to five years before) divided by person time at risk. We used a Poisson regression model to examine prevalence and incidence ratios by sex, age group and calendar year. When comparing age groups, we adjusted for sex and calendar year; when comparing sex, we adjusted for age group and calendar year, and when comparing calendar years, we adjusted for sex and age group. Third, we utilized data on the annual amount (DDD) of conventional disease-modifying drug and biological disease-modifying drug used in the primary sector and hospital sector combined.

Finally, we constructed contingency tables based on history of comedication use and morbidity in the cohort. We assessed comedications ≤1 year before first-time use of a systemic glucocorticoid and morbidity at any time before first-time use.

All statistical analyses were conducted using SAS version 9.4.

RESULTS

We identified 926,314 users (54% female) of systemic glucocorticoids. Median age at first-time use was 55 years (interquartile range: 39 to 69 years) (Table 1). The most frequent generic type of systemic glucocorticoid prescribed was prednisolone (53%), followed by betamethasone (25%), and methylprednisolone (14%) (Table 1).

Systemic glucocorticoid and disease-modifying drug use

The prevalence of systemic glucocorticoid use was approximately 3% each year (Figure 1a). From 1999 to 2014 we observed a 6% decrease in annual prevalence [adjusted prevalence ratio: 0.94 (95% CI: 0.94, 0.95) (Table 2)]. The incidence remained constant at 1.4/100 p-y from 1999 to 2014 (Figure 1c) [adjusted incidence ratio of 1.00 (95% CI: 1.00, 1.03) (Table 2)]. Prevalence and incidence were higher in women than in men (Figure 1). Among the elderly population, the prevalence was 6.7%-7.7% and the incidence was 2.6/100 p-y - 2.8/100 p-y in the 60-79 year age group, and the prevalence was 9.7%-11% and the incidence was 3.0/100 p-y – 3.6/100 p-y among persons aged ≥80 years (Figure 1). The incidence increased slightly among persons aged ≥80 (Figure 1D).

From 1999 to 2014, we observed an increase in use of disease-modifying drugs to treat the underlying inflammatory diseases, including methotrexate, azathioprine, tumor necrosis factor (TNF)-alpha agents (Figure 2), and rituximab, abatacept, tocilizumab and ustekinumab (Figure 2c).

Use of comedications

Prescription drugs redeemed most frequently ≤1 year prior to initial use of a systemic glucocorticoid were: antibiotics [450,613 persons (49%)], agents used to treat cardiovascular conditions [352,125 persons (38%)], NSAIDs [338,367 persons (37%)], agents used to treat asthma/COPD [194,290 persons (21%)], opioids [177,573 persons (19%)], non-opioid analgesics [159,505 persons (17%)], and antidepressants [117,666 persons (13%)] (Figure 3).

Morbidity

Assessment of morbidity leading to hospital contacts at any time prior to first-time use of a systemic glucocorticoids showed that cardiovascular and pulmonary diseases and cancer were prevalent: 172,400 (19%) had cardiovascular disease including hypertension in 90,721 persons (9.8%), ischemic heart disease in 22,825 persons (2.5%), peripheral artery disease (PAD) present in 17,043 persons (1.8%), and stroke present in 39,095 persons (4.2%). 158,658 persons (17%) had a pulmonary disease, with COPD present in 58,114 persons (6.3%). As well, 122,629 persons (13%) had a recorded cancer diagnosis (Figure 4).

DISCUSSION

In this 15-year nationwide study, we found a high (≈ 3%) annual prevalence and incidence (≈1.4/100 p-y) of systemic glucocorticoid use. Glucocorticoid use was more prevalent in the elderly, with prevalence reaching 11% in persons aged ≥80 years and a slightly increase in incidence from 1999 to 2014. As expected, the prevalence of comedication and morbidity was high prior to glucocorticoid use.

Prior studies from the United Kingdom (U.K) (1989-2008), the United States of America (USA) (1999-2008), Iceland (1995-1996), Denmark (1999-2015) and France (2007-2014) have estimated the prevalence of glucocorticoid use to range between 0.5% to 17% depending on calendar year, setting and methodology (16-22). The study from the USA (20) and the U.K (19) reported prevalence of oral glucocorticoid use at approximately 1%, and this lower figure may partly be explained by methodological differences. First, our study investigated all systemic glucocorticoids (oral and injectable formulations) as opposed to only oral glucocorticoids (19, 20). Second, we estimated annual prevalence while previous studies estimated point prevalence (19, 20). Third, the U.K study investigated long-term use (≥ 3 months) (19). The study from France reported an annual prevalence of 17% (22). Altogether, glucocorticoid use seems to vary across countries. Compared to the prior Danish study (21), which lacked individual-level data, this current study added important information on incidence use, comedication and morbidity.

Despite improved awareness of adverse effects and increased use of more targeted treatments, glucocorticoid use remains a mainstay of therapy of many inflammatory diseases. Therefore, the clinical challenge of how to manage and prevent adverse effects of glucocorticoids continues. This involves e.g. prevention and treatment of glucocorticoid-induced osteoporosis, glucocorticoid induced hyperglycaemia and diabetes and guidelines about the assessment and management of adrenal insufficiency during and after glucocorticoid treatment (8, 11, 13, 14, 21). This challenge may increase as incident use among elderly increases. In addition, several clinical concerns arise when morbidity and comedication use is high. Concomitant use of NSAIDs and glucocorticoids increases risk of gastrointestinal haemorrhage (37% in our study) (28) and prior/current psychiatric disease increases risk of psychiatric adverse effects (13% are taking antidepressants prior to

glucocorticoid initiation) (15). Also, special caution is mandated in patients with incipient and overt diabetes (4.5 % are taking oral antidiabetics or insulin prior to glucocorticoid initiation) (7).

We conducted a population-based nationwide study with complete data on medication use, but our study also has limitations. First, data on the use of systemic glucocorticoids and comedications relied on redeemed prescription as an approximation of use, without evaluation of adherence. Second, when patients are treated in hospital setting pharmacological treatment is so far not retrievable at an individual level in our national registries. Third, we were able to capture morbidity only in hospital settings (inpatient and outpatient clinics), excluding primary health care. In addition, we were not able to identify the indication for glucocorticoid treatment. Moreover, the validity of discharge diagnoses recorded in the DNPR is heterogeneous (27). Finally, we did not compare medication use and morbidity among systemic glucocorticoid users to people not treated with glucocorticoids.

In conclusion, our findings suggest a continuously widespread use of systemic glucocorticoids, especially in the elderly. This calls for a more comprehensive approach to prevent complications to glucocorticoid therapy, including the risk of adrenal insufficiency, which should be spearheaded by the endocrine community.

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Author contribution statement: KL, IP, JOLJ, and HTS made primary contributions to conception of the study and wrote the manuscript. KL performed statistical analyses. KL, IP, JOLJ, and HTS contributed to the interpretation of results and revised the manuscript critically. All authors approved the final manuscript. HTS is the guarantor for this study.

Ethics Approval: This study was approved by the Danish Data Protection Agency (Record number: 2016-051-000001, serial number 448)

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FIGURES

Figure 1. Prevalence (%) and incidence (per 100 person years) of systemic glucocorticoid use, Denmark 1999-2014. (A) Prevalence (%) in the overall population and stratified by sex, (B) prevalence stratified by age group, (C) incidence (per 100 person years) in the overall population and stratified by sex, (D) incidence (per 100 person years) stratified by age group.

Figure 2. Amount of annual disease-modifying drugs use expressed in defined daily dose (DDD), Denmark 1999-2014. (A) Conventional disease-modifying drugs. (B) Tumor necrosis factor (TNF)-alpha agents. (C) Other biological agents.

Footnote: Methotrexate and rituximab are not expressed in DDD but gram (active substance). Use of methotrexate increased from 2,007 gram in 1999 to 6,225 gram in 2014. Use of rituximab increases from 1,000 gram in 2004 to 10,000 gram in 2014.

Figure 3. Frequency of comedication use assessed ≤1 year before initial use of a systemic glucocorticoid.

Figure 4. Frequency of morbidity assessed any time before initial use of a systemic glucocorticoid.

Footnote: COPD= Chronic pulmonary disease. PAD= Peripheral artery disease. RA= Rheumatoid arthritis. PMR/GCA= Polymyalgia rheumatica/Giant cell arthritis.