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Title

Long-term oral prednisolone exposure in primary care for bullous pemphigoid: population-based study

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Abstract

Background

Oral prednisolone is the mainstay treatment for bullous pemphigoid, an auto-immune blistering skin disorder affecting older people. Moderate to high dose treatment is often initiated in secondary care, but then continued in primary care.

Aim

To describe long-term oral prednisolone prescribing in UK primary care for adults with bullous pemphigoid 1998-2017.

Design and setting

A prospective cohort study using routinely collected data from the Clinical Practice Research Datalink, a primary care database containing the healthcare records for over 17 million people in the UK.

Method

Oral prednisolone exposure was characterised in terms of the proportion of individuals with incident bullous pemphigoid prescribed oral prednisolone following their diagnosis and the duration and dose of prednisolone.

Results

2,312 (69.6%) of 3,322 people with bullous pemphigoid were prescribed oral prednisolone in primary care. The median duration of exposure was 10.6 months (IQR 3.4 to 24.0). Of prednisolone users, 71.5% were continuously exposed for >3 months, 39.8% for >1 year, 14.7% for >3 years, 5.0% for >5 years, and 1.7% for >10 years. The median cumulative dose was 2,974mg (IQR 1,059 to 6,456). Maximum daily doses were ≥10mg/day in 74.4% of users, ≥20mg/day in 40.7%, ≥30mg/day in 18.2%, ≥40mg/day in 6.6%, ≥50mg/day in 3.8%, and ≥60mg/day in 1.9%.

Conclusions

A high proportion of people with incident bullous pemphigoid are treated with oral prednisolone in UK primary care. Primary and secondary care should address steroid-sparing alternatives and, where switching is not possible, ensure prophylactic treatments and proactive monitoring of potential side-effects are in place.

Keywords

Bullous pemphigoid, prednisolone, prescriptions, primary health care, corticosteroid, Clinical Practice Research Datalink

How this fits in

Bullous pemphigoid is an autoimmune blistering skin disorder that generally affects older people and is associated with three-fold increase in mortality. Although oral prednisolone has been considered the mainstay of treatment for decades, its long-term use in primary care is poorly characterised. 69% of people with incident bullous pemphigoid were prescribed oral prednisolone in primary care, at considerable doses and durations of exposure. As they may be on oral prednisolone for prolonged periods of time, conversations between primary and secondary care physicians involved in their care should address steroid-sparing

alternatives and, when switching is not possible, ensure prophylactic treatment (e.g., bone sparing treatments) and proactive monitoring of side effects are in place.

Main text

Introduction

Bullous pemphigoid is an autoimmune skin disease, characterised by the formation of intensely itchy blisters, that largely affects older people. Approximately 3,500 people are diagnosed with bullous pemphigoid for the first time in England every year, and the diagnosis is associated with approximately three-times increased risk of death in the first two years.(1, 2) Additionally, the diagnosis is associated with increased risk of autoimmune conditions (e.g., systemic lupus erythematosus), neurological conditions (e.g., Parkinson's disease), cardiovascular conditions (e.g., hypertension), and other skin conditions (e.g., psoriasis).(3-5)

Oral prednisolone has traditionally been the first-line systemic treatment for bullous pemphigoid for decades.(6, 7) In recent years, the benefit of safer alternatives has been demonstrated including superpotent topical corticosteroids and anti-inflammatory antibiotics (e.g., doxycycline)(8, 9) but systemic steroids are still widely used. Although effective, prednisolone exposes an already vulnerable group to an increased risk of conditions such as osteoporosis and diabetes.(10, 11) Patients may be initiated on moderate to high doses of oral prednisolone by direct care clinicians upon the diagnosis of bullous pemphigoid in primary or secondary care settings. Patients referred onwards to secondary care for diagnosis and treatment of bullous pemphigoid typically have their long-term management shared jointly between primary and secondary care teams.

Characterising oral prednisolone exposure allows us to better understand the iatrogenic risks posed to people with bullous pemphigoid. The long-term use in this population is poorly understood, and the little available evidence is based on small studies involving hospital-based patients (Table 1). Routinely collected health data from primary care, in the form of the Clinical Practice Research Datalink (CPRD), provides an opportunity to address this research gap using a large population-based sample that is broadly representative of the UK.(12) We aimed to examine prescriptions for oral prednisolone issued in UK primary care for incident cases of bullous pemphigoid.

Methods

Study design and data source

This was a prospective cohort study using routinely collected health data from the CPRD. The CPRD is a longitudinal database of UK general practices containing the anonymised diagnosis, referral, prescription, and vaccination data of approximately 17 million people, with a current coverage of approximately 2.7 million (4%) of the UK population. Although bullous pemphigoid is predominantly diagnosed in secondary care, the diagnosis is subsequently transcribed from discharge or specialist clinic letters into the CPRD using Read codes.(13) For this study we used only practices recording data using VISION software (CPRD GOLD). The data in the CPRD have repeatedly been shown to be of good research quality.(14) At the practice-level, participating practices are audited to confirm data quality. At the patient-level, records are assessed and data checks are conducted to ensure that the record meets prespecified quality standards.

This work follows the Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines.(15)

Study population

The study population comprised adult men and women with incident bullous pemphigoid diagnoses between January 1998 and December 2017, selected using previously described methods.(1, 16) In short, a validated algorithm was implemented to identify people with a code for bullous pemphigoid (M145), pemphigoid (M145.00), or pemphigoid NOS (M145z00) in their clinical records. This approach has a positive predictive value of 93.2% (95% CI 91.3% to 94.8%).(16) The bullous pemphigoid index date was the date the diagnosis was first recorded.

To identify people for whom prednisolone might have been prescribed for alternative indications, only people with at least 12 months data prior to the bullous pemphigoid index data were eligible. In order to allow sufficient time to capture prescriptions (under the assumption that initial treatment would be prescribed in secondary care and therefore wouldn't appear in the CPRD), people with less than six months follow-up after their bullous pemphigoid index date were excluded.

Observation period

People were followed up from their bullous pemphigoid index date until the earliest of the date: (i) the person left the practice, (ii) the person died, (iii) the practice last contributed data to the CPRD, or (iv) 31 December 2017.

Oral prednisolone prescriptions

All prescriptions for oral prednisolone (Codes in Supplementary Table S1) during the observation period were identified. We focused only on prescriptions issued after the bullous pemphigoid index date under the assumption that these would reflect long-term management following the diagnosis.

Prednisolone dose and duration were extracted when available and imputed when missing. These data were often missing when prescriptions were issued with information restricted to the free text field, such as "Take as indicated by your dermatologist". Implausible and missing values were handled using the DrugPrep algorithm(17) with the decisions described and validated by Joseph et al.(18) (Supplementary Table S2). Cleaning oral glucocorticoid prescriptions in this way has a sensitivity of 84.2% (95%CI 68.7 to 94.0%) and specificity of 87.5% (95%CI 73.2 to 95.8%) for predicting patient-reported current glucocorticoid use.(18)

Alternate indications for oral prednisolone

Oral prednisolone can be prescribed for other indications besides bullous pemphigoid, such as rheumatoid arthritis or asthma. To understand the proportion of people that may have been prescribed prednisolone for reasons other than bullous pemphigoid, those with a Read code for an alternate indication in the 12 months preceding their bullous pemphigoid index date were identified. The code lists were drawn from Kuan et al(19) (Supplementary Table S3).

Statistical analysis

The proportion of people prescribed oral prednisolone following their bullous pemphigoid index date was determined (referred to as users). The proportion of users that may have been prescribed prednisolone for an alternate indication was determined (i.e., people with a Read code for an alternate indication and a prescription for oral prednisolone in the 12 months preceding bullous pemphigoid).

For each prednisolone user, the number of prescriptions, total follow-up time, follow-up time on prednisolone, and proportion of follow-up on prednisolone was determined. The duration of continuous exposure, defined

as prescriptions with less than 15 days between the end of one and the start of the next, was determined for each person. The number of periods of continuous exposure were determined per person and summarised across the population. The proportion continuously exposed for longer than 3 months, 1 year, 3 years, 5 years, and 10 years were determined. For these, the denominator included only people with follow-up longer than the duration of interest (i.e., longer than 3 months, 1 year, 3 years, 5 years, and 10 years, respectively).

Finally, the doses of oral prednisolone were examined. We determined the median daily dose for all prescriptions. The proportion of users prescribed ≥10 mg/day, ≥20mg/day, ≥30 mg/day, ≥40 mg/day, ≥50 mg/day, and ≥60 mg/day was determined. The cumulative dose of prednisolone throughout the whole observation period was calculated per person, and the median determined across the population. The average dose whilst on prednisolone was determined by dividing the cumulative dose by the duration of exposure.

A sample size calculation was not conducted as this was a descriptive study using all available data. Population summary measures were presented as the median (IQR) of continuous variables or number (proportion) per categorical measure. Analyses were conducted with Stata 16 (2019; StataCorp LLC, College Station, TX, USA).

Results

Study population

There were 4,437 people with incident bullous pemphigoid in the study period (Figure 1). 762 people with less than six months follow-up after their index date were excluded from the study, of whom 499 died. A further 353 people without 12 months of data prior to their index date were excluded. As such, the study population comprised 3,322 people with incident bullous pemphigoid with at least 12 months of data before and 6 months of data after their index date. They were identified from 667 practices, with a median of 4 people with bullous pemphigoid per GP practice. The median age at first recording of bullous pemphigoid was 79.7 (IQR 71.6 to 86.0) years and 1,858 (55.9%) were women. Median duration of follow-up was 3.1 years (IQR 1.5 to 5.7) and ranged from 6 months to 18 years. Overall, the population represents 13,758.2 person-years of follow-up.

Prednisolone users

Overall, 2,312 (69.6%) people were prescribed oral prednisolone after their bullous pemphigoid index date (users). They were followed for 9,506.0 person-years, of which 9.3 person-years were on prednisolone. The median number of months individuals spent on prednisolone was 10.6 (IQR 3.4 to 24.0), representing a

median of 0.11% (IQR 0.02 to 0.24) of their follow-up. The median number of prescriptions for prednisolone per patient was 15 (IQR 8 to 26).

Of the users, only 321 (13.9%) people had complete data for all prescriptions. For the remaining people, the dose, start date, or treatment duration were imputed for at least one prescription. Eighty-eight (3.8%) of the users had a Read code for an alternate indication (e.g., rheumatoid arthritis) and a prednisolone prescription in the 12 months before bullous pemphigoid.

Duration of continuous exposure

The median number of periods of continuous exposure was 2 (IQR 1 to 3) per patient and they ranged from 1 day to 12 years duration. Overall, 71.5% of users were on prednisolone continuously for >3 months, 39.8% for >1 year, 14.7% for >3 years, 5.0% for >5 years, and 1.7% for >10 years (Figure 2).

Oral prednisolone doses

The median daily dose across all prescriptions was 10 mg/day (IQR 5 to 13). 1,721 (74.4%) of users were prescribed a maximum dose of ≥10 mg/day, 941 (40.7%) were prescribed ≥20 mg/day, 420 (18.2%) ≥30 mg/day, 153 (6.6%) ≥40 mg/day, 87 (3.8%) ≥50 mg/day, and 44 (1.9%) ≥60 mg/day (Figure 2) at any point during the observation period.

The median cumulative dose during follow-up was 2,974 mg (IQR 1,059 to 6,456). Focusing only on the duration of follow-up where the person was on a prednisolone prescription, the average daily dose was <2.5mg/day for 11 (0.5%) people, 2.5-5mg/day for 152 (6.6%) people, 5-7.5 mg/day for 351 (15.2%) people, and over 7.5 mg/day for 1,798 (77.8%) people.

Discussion

Summary

We have described oral prednisolone prescribing in UK primary care for people with bullous pemphigoid. Of all people with new diagnoses of bullous pemphigoid identified 1998-2017, 69.6% were prescribed oral prednisolone in primary care following their diagnosis. Under the assumption that the initial high-dose regimens of prednisolone are more likely to be issued in dermatology clinics rather than primary care, and

ongoing prescriptions may not exclusively be issued in primary care, our findings likely underestimate both the duration of exposure and dosages of prednisolone and should be viewed as the minimum exposure.

We found that 71.6% of users were exposed to prednisolone continuously for over three months, whilst 39.8% were on prednisolone for over a year. A small subset (1.7%) were on prednisolone continuously for over 10 years. Most people (74.4%) received daily doses greater than 10mg/day at some point. The prescriptions totalled a median cumulative dose of 2,974 mg throughout the study period and, for 78% of the people, an average daily dose >7.5mg/day during active periods of prescriptions.

Despite only presenting the minimum estimated exposure, these levels are sufficient to place people with bullous pemphigoid at risk of corticosteroid-associated adverse events.(20, 21) Strict monitoring and proactive management are required to minimise the risks to this population.

Strengths and limitations

Strengths of the present work include a large sample size, people with bullous pemphigoid identified from a source population that is broadly representative of the UK,(12) and the implementation of validated methods for identifying bullous pemphigoid and preparing the prescription data. The algorithm used to identify people with bullous pemphigoid has a positive predictive value of 93.2%,(16) thus indicating that the population analysed likely have bullous pemphigoid. The approach to preparing the prescriptions is validated and shown to accurately classify current oral corticosteroid status (on/off) for 86% of cases.(18) Daily dose estimates generated from this approach are imprecise but not significantly biased, with a mean absolute difference in estimated and reported doses of 3.2 (SD 4.2) mg/day.(18) Finally, we believe our work largely comprises individuals that were prescribed prednisolone for bullous pemphigoid rather than for other indications. Only 3.8% of the users had (i) a record for an alternate indication for oral prednisolone *and* (ii) a prescription for oral prednisolone in the 12 months preceding bullous pemphigoid.

Limitations largely relate to the nature of the data used. First, although validated approaches for identifying cases and exposure were used, the findings may be subject to misclassification and measurement error. This is further compounded by the large proportion of missing data, affecting at least one prescription for 86.1% of people. Second, we were only able to examine prescriptions issued in primary care. As such, we only present the minimum estimated exposure to prednisolone. In addition, the absence of information regarding the

timing and duration of secondary care follow-up meant that we could not describe the interplay between primary and secondary care prescribing of prednisolone. Third, we were not able to capture and describe tapering regimens for prednisolone due to insufficient granularity in the data. Fourth, we only examined oral prednisolone and did not consider other systemic oral corticosteroids, such as betamethasone, and may therefore underestimate the total corticosteroid exposure. Finally, exclusion of people with less than six months follow-up may have limited the external validity of our sample as death was the commonest reason for insufficient follow-up. However, it was felt that including people with less than six months follow-up would artificially lower the estimated exposure to prednisolone as there was insufficient time for the prescriptions to pass from dermatology clinics to general practice.

Comparison with existing literature

We report the first population-based cohort study to examine the prescribing patterns of oral prednisolone for bullous pemphigoid in UK primary care. Recent evidence on oral corticosteroid use for bullous pemphigoid in the UK is based on a national audit completed by members of the British Association of Dermatologists. In this, 85.5% (448 of 524) of those with bullous pemphigoid diagnoses were prescribed an oral corticosteroid by their dermatologist at some point during their management.(22) We report that a more modest 69.6% of people are prescribed prednisolone in primary care, although this discrepancy may be largely attributed to the different settings. The higher proportion from the survey suggests that some people are exposed to prednisolone only in secondary, and not primary, care. It may be that these people commence oral prednisolone, which is then stopped in favour of an alternate treatment, because of disease resolution, or death. Alternatively, they may continue to be prescribed oral corticosteroids in secondary care.

Worldwide, several studies have reported oral prednisolone use in people with bullous pemphigoid. Our findings are largely in keeping with the proportion of users in the previous literature, although we report substantially lower doses than elsewhere (Table 1). Again, this may be due to differences in the setting and timing of prescriptions (i.e., initial vs long-term treatment). In clinical practice, oral corticosteroids are used as a slowly reducing regimen for many months. Previous studies have captured the high initial doses prescribed. Our work has extended beyond this initial period and captured high maximum doses (≥60mg/day in some) potentially indicative of initial doses and lower maintenance doses (e.g., median daily doses <10mg/day) potentially reflecting tapering regimens. Further interpretation of earlier evidence is hindered by the small

population sizes and largely hospital-based setting of previous research which generally did not extend beyond the initial management.

Implications for research and/or practice

Those with bullous pemphigoid are a clinically vulnerable group due to their older age (median age: 79.7 years) and significant comorbidities on disease recording, including hypertension, diabetes mellitus, heart failure, and osteoporosis.(23) There is therefore a need for careful consideration of additional risks posed to this population. There is evidence of a dose-dependent relationship between the cumulative dose of prednisolone and sleeping problems, acne, skin bruising, mood problems, cataracts, hyperglycaemia, and bone fractures.(24) Focusing specifically on fracture risk, a daily dose of 7.5 mg/day approximately doubles the chance of developing a hip and vertebral fracture compared to less than 2.5 mg/day.(21) This risk is evident even within 3-6 months of starting.(20) As such, clinicians are exposing people with bullous pemphigoid to substantial iatrogenic risks due to prednisolone prescribing. Although these risks are outweighed in the short term by the urgent need to control the disease, our work shows that the exposure to prednisolone extends beyond the initial regimens prescribed in dermatology clinics.

Although general practitioners will often not be involved in the initial aggressive management of bullous pemphigoid, they may be tasked with prednisolone prescribing in the longer term. We urge clinicians to be mindful that this population, who may already be frail due to age and significant comorbidities, may be on large doses of prednisolone for substantial periods of time. Strict monitoring and careful consideration of prophylactic treatments, such as bone protection therapies, are essential for their long-term management. In addition, conversations between primary and secondary care should take place to consider steroid-sparing alternative treatments such as doxycycline. In 2017, doxycycline was shown to be non-inferior to oral corticosteroids for the management of bullous pemphigoid.(8) This will likely impact on clinicians' practices, but such changes will not have been captured by the present work (observation period 1998-2017). Further research may be needed to re-explore systemic steroid prescribing in patients post 2017.

Future research should also expand on our work to examine steroid-related outcomes (e.g., hip and pelvis fractures) in people with bullous pemphigoid and to determine whether adequate monitoring and prescription of prophylactic treatment (e.g., bisphosphonates) occurs.

Additional information

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Ethical approval

The present study was approved by the Independent Scientific Advisory Committee for the CPRD (ISAC protocol no 18_224).

Data availability

The data can be requested from www.cprd.com

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Competing interests

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Figure legends

Figure 1. Identification of the study population of adults with incident bullous pemphigoid from the CPRD

Figure 2. Proportion of people (users) continuously exposed to oral prednisolone for longer than 3 months, 1 year, 3 years, 5 years, and 10 years. The denominator per duration includes only people with follow-up durations exceeding the duration of interest

Figure 3. Proportion of people (users) prescribed a maximum daily dose of oral prednisolone ≥10mg,≥20mg,≥30mg,≥40mg,≥50mg,≥60 mg at any point during the observation period

Table

Table 1. Proportion of patients with bullous pemphigoid exposed to oral prednisolone as presented in published studies, presented alongside dose and duration information

Publication	Country	Setting	Years	n	Treatment timing	Proportion on oral prednisolone	Additional dose and duration detail
Balestri 2017(25)	Italy	Clinic	2008-2012	53	Initial	96.2%	Dose range: 0.5-0.75 mg/kg/day
Kremer 2017(26)	Israel	Hospital	2008-2014	104	Initial	78.1%	Mean dose: 57.3 mg/day (range 30-70 mg/day)
Zhang 2013(27)	China	Hospital	2005-2010	94	Initial	85%	Maximum dose: range 20-80 mg/day
Esmaili 2012(28)	Iran	Hospital	1987-2007	122	Initial	73.8%	Mean dose: 60.38±21.21 mg/day (range 5-120 mg/day)
Kulthanan 2011(29)	Thailand	Clinic	1991-2009	58	Initial	89.7%	Mean cumulative dose to achieve remission: 0.05 g/kg
Serwin 2007(30)	Poland	Hospital, clinic	2000-2006	35	Initial	68.6%	Dose range: 40-60 mg/day
Nanda 2006(31)	Kuwait	Clinic	1991-2005	41	Initial	100%	
Tan 2018(32)	Singapore	Hospital	2004-2012	100	Anytime	96%	Mean duration: 11.6 months (range 1 week to 60 months)
Wong 2002(33)	Singapore	Hospital	1998-1999	59	Initial	76%	Mean dose: 31.2 mg/day (range 15 to 60) when used as monotherapy
Chang 1996(34)	Taiwan	Hospital	1977-1994	86	Initial	83.7%	Mean dose: 54.1 mg/day
Garcia-Doval 2005(35)	Spain	Hospital	1998-2003	26	Unclear	53.9%	Mean daily dose at start of therapy: 34 mg (SD 9.8) (range: 20–50) Mean duration: 20 months (SD 12)

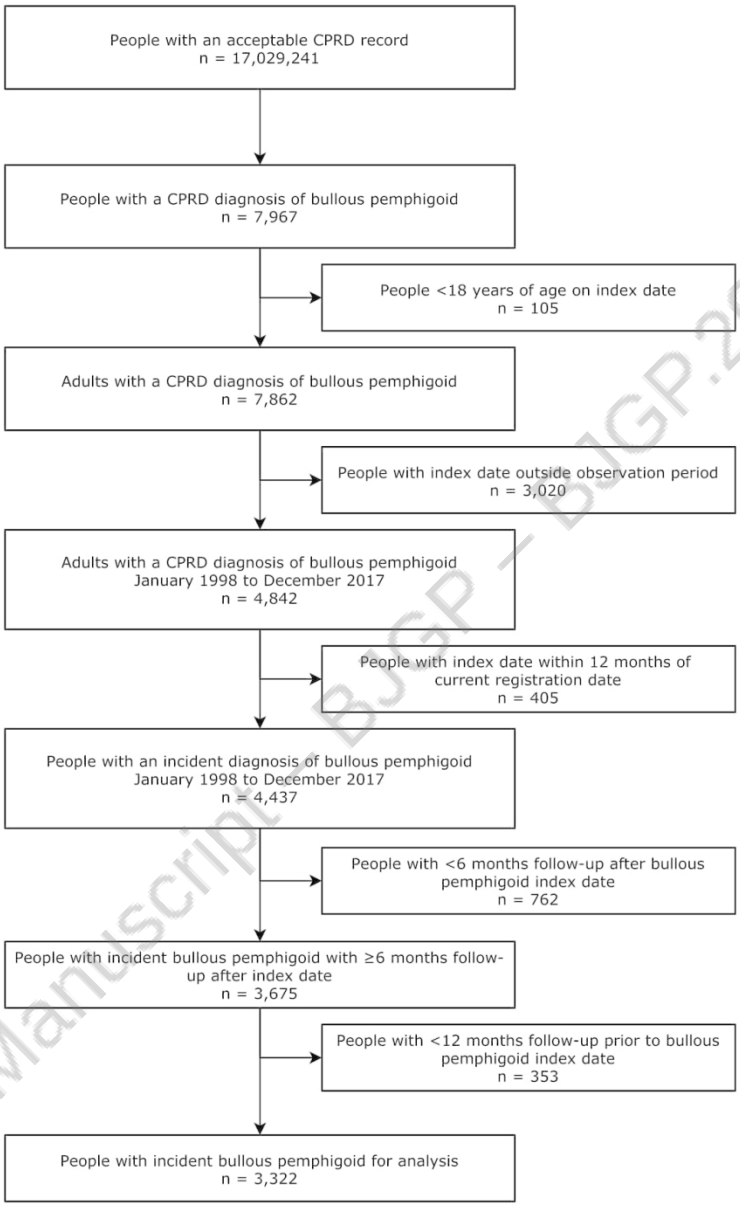

Figure 1. Identification of the study population of adults with incident bullous pemphigoid from the CPRD

376x612mm (72 x 72 DPI)

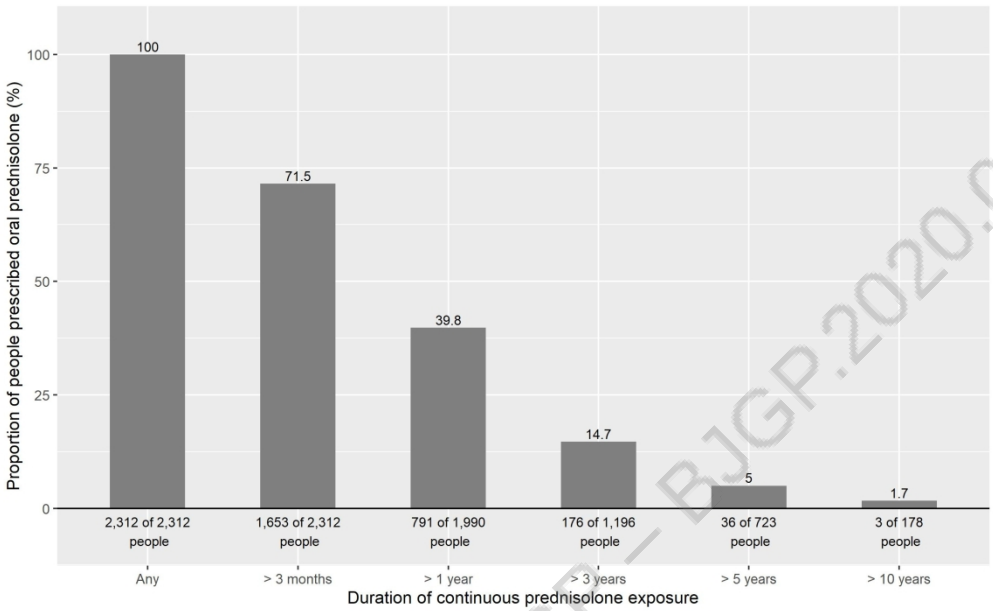

Figure 2. Proportion of people (users) continuously exposed to oral prednisolone for longer than 3 months, 1 year, 3 years, 5 years, and 10 years. The denominator per duration includes only people with follow-up durations exceeding the duration of interest

228x140mm (300 x 300 DPI)

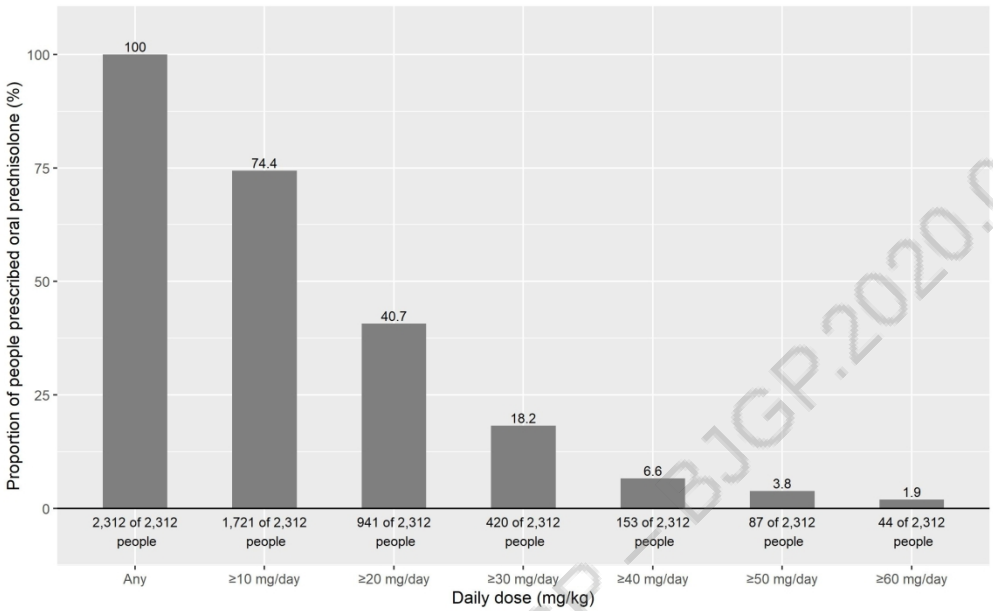

Figure 3. Proportion of people (users) prescribed a maximum daily dose of oral prednisolone ≥10mg,≥20mg,≥30mg,≥40mg,≥50mg,≥60 mg at any point during the observation period

228x140mm (300 x 300 DPI)