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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Montelukast use—a 19-year nationwide drug utilisation study

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Abstract
Purpose Montelukast is a leukotriene receptor antagonist used in asthma and rhinitis treatment. Despite being marketed nearly two decades ago, little is known about its utilisation pattern.
Methods Using the Danish National Prescription Registry, we identified subjects filling a montelukast prescription between 1998 and 2017. Using descriptive statistics, we reported the development in incidence, and prevalence, as well as a measure of treatment duration, and concomitant use of asthma- or anti-allergic therapy.
Results We identified 147,247 individuals filling 1,327,489 montelukast prescriptions. A total of 54,349 users (37%) filled only one montelukast prescription. The prevalence increased from 0.9/1000 persons in 1998 to 3.3/1000 persons in 2016. The rate of new users reached its maximum of 2.1/1000 person-years in 2009. Among new montelukast users, 28% were still users after 1 year. Among all montelukast initiators, 60% filled at least one prescription of short-acting beta-2-agonists (SABA) up to a year prior to montelukast initiation, and 49% filled a prescription of inhaled corticosteroids (ICS). Only 0.8% (n = 1148) of all individuals initiated montelukast without a redeemed prescription of short- or long-term inhalation therapy, systemic antihistamines, or nasal topical anti-allergic treatment.
Conclusions The usage of montelukast has increased over threefold since its market entry in 1998, mainly driven by an increased number of prevalent users. The majority of individuals who initiated montelukast filled a prescription of SABA up to a year prior to montelukast initiation, whereas almost half filled a prescription of ICS.

Keywords Pharmacoepidemiology · Montelukast · Asthma

Introduction

Asthma is the most common chronic disease among children and young adults worldwide, and it is estimated that 300 million people suffer from the disease [1]. The disease is characterised by a changeable symptom profile including wheezing, cough, shortness of breath and variable expiratory airflow limitation [1].

Leukotriene receptor antagonists (LTRA) were marketed in 1998 as non-steroid oral add-on therapy to inhaled corticosteroids (ICS) in patients with mild to moderate chronic asthma. LTRAs specifically block cysteinyl leukotriene receptor type 1, which plays a major role in the pathophysiology of asthma by mediating mucus inflammation which induces bronchoconstriction [2]. Studies have confirmed the benefits of LTRAs in alleviating symptoms of airway obstruction and reducing airway eosinophilic inflammation [3]. Although LTRAs are considered less effective than ICS, they may be appropriate for initial controller treatment for some patients

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using low dose controller medication in combination with as-needed reliever medication, according to the Global Initiative for Asthma guideline [1].

Since entering the market, the indication for LTRA treatment has been expanded to include exercise-induced asthma, and symptomatic treatment of seasonal and perennial rhinitis [4]. However, there have also been indications of off-label use [5] including treatment of nasal polyposis [6], allergic bronchopulmonary aspergillosis [7] and particularly in chronic obstructive pulmonary disease (COPD) [8]. Although COPD is not a therapeutic indication of montelukast, studies have shown that when used as add-on in routine treatment protocol, montelukast improves pulmonary function tests, dyspnea scores and quality-of-life scores in patients with stable COPD [9].

Despite that montelukast, the most commonly prescribed LTRA, has been on the market for almost two decades, very little is known about its pattern of usage over time [10]. Few studies have focused on either on specific populations [11–13] or users with a specific diagnosis [14, 15], but none have assessed the usage over time in an entire nation.

Therefore, we aimed to describe the use of montelukast treatment in Denmark since its market entry in 1998, using standard drug utilisation statistics developed for individual-level prescription data [16].

Methods

In this drug utilisation study, we described the outpatient use of montelukast during the period from 1 March 1998 to 31 December 2016, among the entire Danish population, including assessment of duration of use and potential off-label use of montelukast.

Data sources

We retrieved data from three Danish nationwide registers: The Register of Medicinal Products Statistics [17], The Danish National Patient Register [18] and the Danish Civil Registration System [19]. Due to the unique Central Persons Register (CPR) number, and the Danish National Health Service provides tax-supported health care for the entire Danish population, it is possible to conduct true population-based register-linkage studies covering the entire population [19]. Therefore, users can be followed using the CPR number across pharmacies and thus all dispensings for an individual subject during the study period were included. For a detailed overview of the three registers, please refer to Supplementary Appendix 1.

Study drugs

Montelukast (ATC, R03DC03) is the only LTRA that has been marketed in Denmark. The defined daily dose (DDD) for montelukast is 10 mg, according to the WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD index [20].

We considered each person as a 'current user' on a given day if they had filled a montelukast prescription with enough doses to cover that day. The duration of each prescription was defined as the number of tablets dispensed (i.e., assuming a consumption of one tablet per day), while adding 25% to the duration to account for irregular prescription refills and/or non-compliance. The addition of 25% to the duration of therapy is based on a definition of 80% compliance, which is used as an arbitrary cut-off defining compliance in traditional compliance research [21, 22].

Analysis

We defined users as patients redeeming one or more prescriptions of montelukast in a given year. For each calendar year (1998 up to 2017), we calculated the amount of DDD filled per person.

To describe the trend in amount of montelukast used per person each year, we calculated the total number of users of montelukast per year from 1998 up to 2017 and the total annual amount of DDDs filled within the same period.

We calculated point prevalence proportions, i.e., the number of current users per 1000 in the population, from 1998 up to 2017 using the total population living in Denmark 1 January of each relevant year as the denominator. The sex and age-specific (1-year intervals) prevalence proportion for 2016 was reported.

To describe duration of treatment, we used the 'proportion of patients covered' (PPC) method [23]. In brief, we followed all individuals from the date of their first montelukast prescription. Over time, we estimated the proportion of all subjects still alive after X days that seemingly still used montelukast at that day (defining current use as in the analysis of point prevalence). Thereby, an individual could be regarded as dropped out of treatment at one point in time and later be re-classified as current user upon filling a new prescription. We divided the analysis into the following age groups: 0–18, 19–39, 40–64 and 65–90+ years old.

Stata version 14.1 (StataCorp, College Station, TX, USA) was used for all analyses.

Results

Demographics

During the study period (1 March 1998 to 31 December 2016), 147,247 subjects filled 1,327,489 montelukast prescriptions with a total of 68,443,728 DDDs. A total of 54,349 (37%) individuals filled only one montelukast prescription during the study period, whereas 37,828 (26%), and 62,639 (43%) filled 2–4, and 5+ prescriptions, respectively. The median number of DDDs filled per prescription was 28 (inter-quartile range [IQR] 28–98).

The median age of montelukast initiation was 35 years (IQR 10–57 years). The majority of users were females (54%, $n = 78{,}760$), and women initiated montelukast at a later age than male users (female median age 41 years [IQR 15–59 years], male median age 24 years [IQR 6–53 years], $p < 0.001$). In total, 76% had a Charlson Comorbidity Index of 0, 5.2% had an asthma-related discharge diagnosis 1 year prior to montelukast initiation, and 2.5% had a COPD-related discharge diagnosis; 0.3% had both an asthma- and a COPD-related discharge diagnosis within a year before montelukast initiation. The majority of users (60%) filled at least one prescription of short-acting beta-2-agonists (SABA) up to a year prior to montelukast initiation, and 49% filled a prescription of ICS.

The demographic characteristics of users initiating montelukast are presented in Table 1.

Prevalence, incidence and amount used

The total amount of DDDs was 729,358 in 1998, and 5,459,839 in 2016. The total amount of DDDs used from 1998 to 2016 is presented in Fig. 1.

The number of montelukast users (point prevalence) increased during the study period, from 0.9 per 1000 persons in 1998 to 3.3 per 1000 persons in 2016 (Fig. 2). The full age spectrum for prevalence of montelukast use at the end of the study period (2016) is provided in Fig. 3, showing a bimodal configuration with peaks among 2–10-year category, and again among 50–70 year olds, but with large variation within the individual years.

The incidence rates from 1998 to 2015 show a bimodal curve (Fig. 4). The number of incident users decreased from 1998 to 2004 (from 1.8 per 1000 person-years in 1998 to 0.7 per 1000 person-years in 2004), and increased from 2004 to 2009 where it reached its maximum (2009 incidence rate: 2.1 per 1000 person-years).

Duration of usage

The proportion of montelukast users who followed their initial prescription over time depended on age, as presented in Fig. 5, with persistence increasing with age. Overall, 28% were current users of montelukast a year after filling their first prescription. The lowest proportion still treated after 1 year was among the 18–39-year-old users (21%), whereas 33% of the users aged 65–90+ years were still treated 1 year after their first filled prescription.

Similar results were obtained when stratifying by sex or calendar time (data not shown).

Concurrent medication

Among all users initiating first-ever montelukast, 7.7% filled a prescription of SABA, SAMA or a combination without filling a prescription of LABA, LAMA, ICS (or combinations), nasal topical anti-allergic treatment or systemic antihistamines. In total, 31.7% initiated LABA, LAMA, ICS, SABA and SAMA (or combinations) within a year prior to montelukast initiation (Table 2). Only 0.8% ($n = 1148$) did not redeem a prescription of LABA, LAMA, ICS, SABA, SAMA, systemic antihistamines or nasal topical anti-allergic treatment within a year prior to montelukast initiation. The proportion of montelukast initiators who did not fill a prescription of short- or long-term inhalation therapy increased throughout the study period, whereas the proportion of non-users of short- and long-term inhalation therapy, nasal topical anti-allergic treatment and systemic antihistamines remained stable (Appendix Fig. 1).

Discussion

This is the first study to report a nationwide utilisation of montelukast, a LTRA used in asthma treatment or as symptomatic relief of (allergic) rhinitis. We found an increase in the usage of montelukast, mainly driven by the increased number of prevalent users. The incidence rate showed a bimodal curve over time, with a maximum in 2009, and a steadily increasing point prevalence proportion from 2006 to 2016. The majority of individuals who initiated montelukast filled a prescription of SABA up to a year prior to montelukast initiation, whereas almost half filled a prescription of ICS. Only 0.8% did not fill a prescription of medication, which may be indicative of a relatively limited ‘off-label’ use of montelukast.

The study has several strengths. The nationwide setting allows the analysis of montelukast use in the entire Danish population regardless of socioeconomic or insurance status. The completeness of Danish Register of Medicinal Products Statistics allowed the analyses to be conducted over a 19-year period with no risk of recall bias or dropout [17].

The study’s main limitation was the lack of information regarding treatment indication. We had no information on the diagnoses from general practitioners, where the majority of patients with asthma, rhinitis, systemic allergies and COPD are treated. Instead, we had to use surrogate markers (prescriptions of short- and long-acting inhalation therapy, nasal topical

Table 1 Baseline characteristics of patients initiating montelukast

	All	Age 0–17 years	Age 18–39 years	Age 40–64 years	Age 65–90+ years
Total	(*n* = 147,247)	(*n* = 53,621)	(*n* = 26,893)	(*n* = 42,252)	(*n* = 24,481)
Age, median (IQR)	35 (10–57)	5 (2–11)	30 (23–35)	52 (46–58)	72 (68–78)
Sex					
Female	78,760 (53.5%)	22,201 (41.4%)	16,029 (59.6%)	26,031 (61.6%)	14,499 (59.2%)
Male	68,487 (46.5%)	31,420 (58.6%)	10,864 (40.4%)	16,221 (38.4%)	9982 (40.8%)
Charlson Comorbidity Index (CCI)					
CCI score = 0	112,191 (76.2%)	51,630 (96.3%)	22,562 (83.9%)	28,551 (67.6%)	9448 (38.6%)
CCI score = 1	24,289 (16.5%)	1748 (3.3%)	3767 (14.0%)	10,029 (23.7%)	8745 (35.7%)
CCI score = 2	6521 (4.4%)	187 (0.3%)	377 (1.4%)	2229 (5.3%)	3728 (15.2%)
CCI score ≥ 3	4246 (2.9%)	56 (0.1%)	187 (0.7%)	1443 (3.4%)	2560 (10.5%)
Admissions[a]					
Asthma related	7594 (5.2%)	4335 (8.1%)	1183 (4.4%)	1519 (3.6%)	557 (2.3%)
COPD related	3728 (2.5%)	39 (0.1%)	45 (0.2%)	1185 (2.8%)	2459 (10.0%)
Both asthma- and COPD-related diagnosis	381 (0.3%)	19 (0.0%)	16 (0.1%)	199 (0.5%)	147 (0.6%)
Concurrent medication[ab]					
SABA[c]	88,595 (60.2%)	35,925 (67.0%)	14,607 (54.3%)	23,603 (55.9%)	14,460 (59.1%)
SAMA	2426 (1.6%)	51 (0.1%)	93 (0.3%)	833 (2.0%)	1449 (5.9%)
LABA[d]	22,238 (15.1%)	3104 (5.8%)	3810 (14.2%)	8730 (20.7%)	6594 (26.9%)
LAMA	5020 (3.4%)	13 (0.0%)	137 (0.5%)	1920 (4.5%)	2950 (12.1%)
ICS	72,491 (49.2%)	29,461 (54.9%)	10,922 (40.6%)	19,502 (46.2%)	12,606 (51.5%)
LABA + ICS	34,500 (23.4%)	5410 (10.1%)	8286 (30.8%)	14,195 (33.6%)	6609 (27.0%)
Oral steroids	30,577 (20.8%)	1045 (1.9%)	5949 (22.1%)	13,302 (31.5%)	10,281 (42.0%)
Nasal topical anti-allergic treatment	37,172 (25.2%)	8877 (16.6%)	9625 (35.8%)	13,922 (32.9%)	4748 (19.4%)
Systemic antihistamines	38,752 (26.3%)	10,432 (19.5%)	10,208 (38.0%)	13,301 (31.5%)	4811 (19.7%)

IQR inter-quartile range, *CCI* Charlson Comorbidity Index, *COPD* chronic obstructive pulmonary disease, *SABA* short-acting beta-2-agonists, *SAMA* short-acting muscarinic agonists, *LABA* long-acting beta-2-agonists, *LAMA* long-acting muscarinic agonists, *ICS* inhaled corticosteroids

[a] Up to a year prior to initial montelukast prescription

[b] Percentages may add to more than 100%, as a patient may be counted in more than one category

[c] Including SABA + SAMA combination

[d] Including LABA + ICS, and LABA + LAMA combination

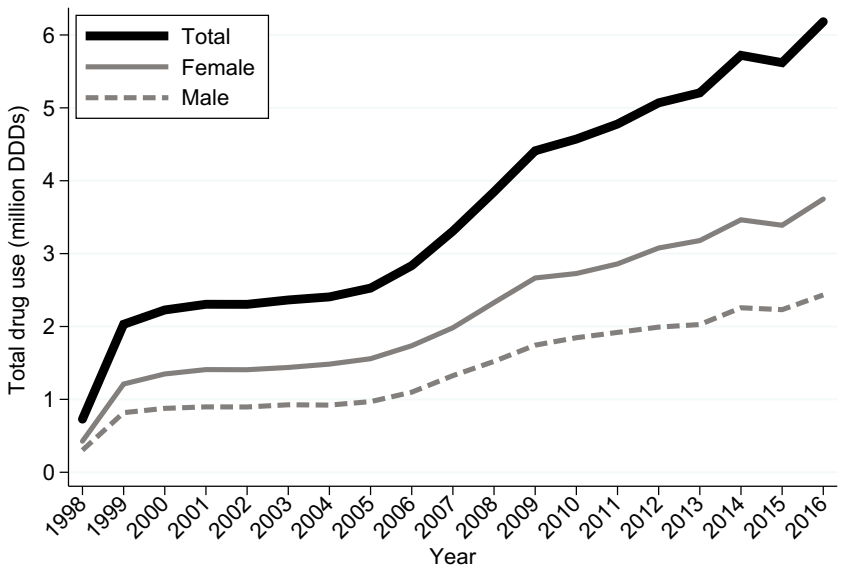

Fig. 1 Total amount of dispensed DDD, specified by sex and year in Denmark from 1998 to 2016

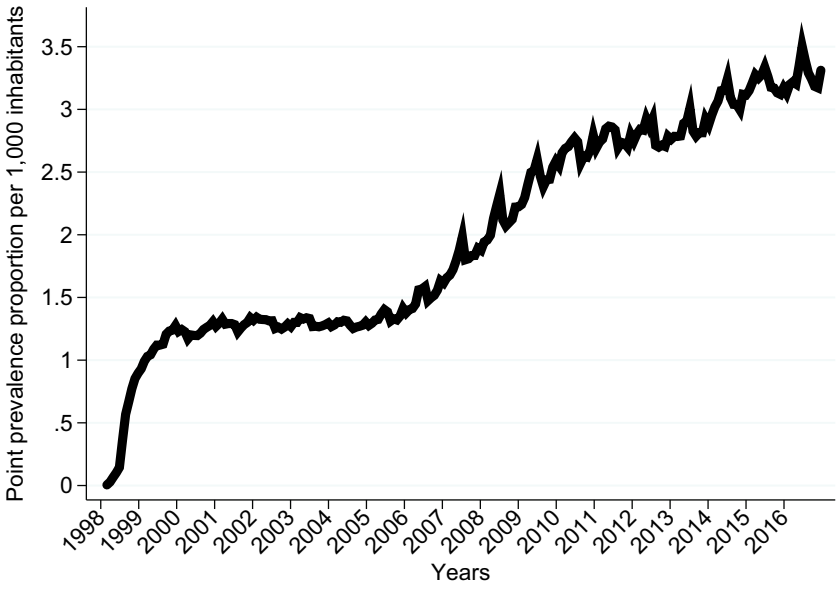

Fig. 2 Overall point prevalence proportion of montelukast use in Denmark from 1998 to 2016

anti-allergic therapy and systemic anti-allergic therapy) to investigate on-label use. In future studies, it would be interesting to further assess the therapeutic indications, e.g., by a questionnaire survey. Furthermore, about 40% of the systemic antihistamine sale are over the counter, and thus not recorded in the register [25]. This could underestimate the number of patients using concomitant montelukast and antihistamine use. However, patients with chronic allergies are granted subsidies for over-the-counter systemic antihistamines in Denmark [17], and are thus recorded in the Danish National Prescription Registry.

The Register of Medical Products Statistics does not contain information on the subject's daily drug use, i.e., prescribed daily dosage. Therefore, we had to use the number of redeemed DDDs adding 25% to the duration of therapy is based on a definition of 80% compliance.

The majority of previous studies have focused on either a specific population, like children [11–13], or users with a specific diagnosis, for example, allergic rhinitis [14], or childhood wheeze (using concurrent SABA treatment as a surrogate marker) [15]. A Paediatric Postmarketing Pharmacovigilance and Drug Utilization Review of montelukast from the Food and Drug Administration in 2014 showed that over a period from 2012 to 2013, approximately 8.8 million children and adults received prescribed montelukast from US outpatient retail pharmacies and 40.8 million montelukast prescriptions were filled [26]. Two thirds of all users were adults, which is also the case in our current study.

Among the paediatric population, prescription for montelukast has increased fourfold in the UK for children from 2000 to 2006, with similar increases in the USA and in Australia [11]. This corresponds to our current study, where the age-specific prevalence proportions have changed during the montelukast marketing period, shifting towards a higher prevalence among paediatric patients from 2005 to 2015. The reason for this is unclear. It could be due to the new insights of treatment in this population [27].

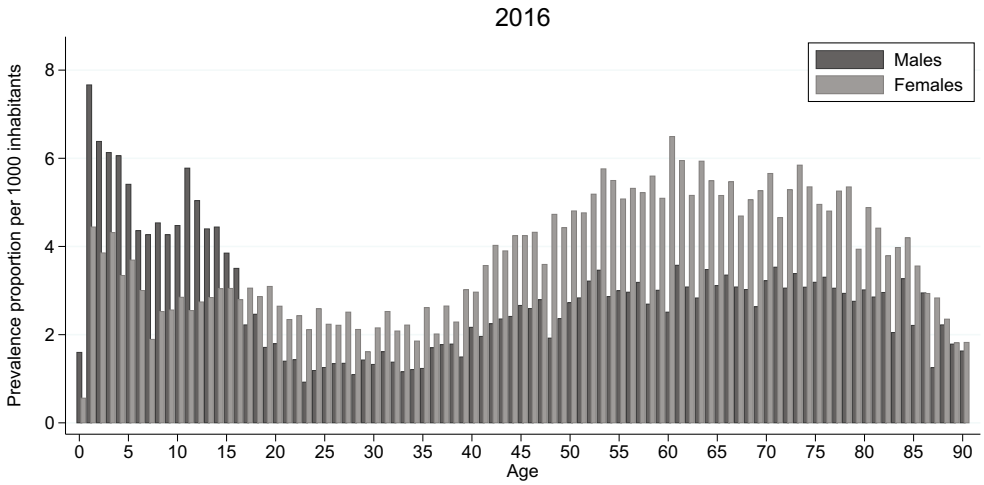

Fig. 3 Age and sex-specific prevalence proportion of montelukast use by end of 2016

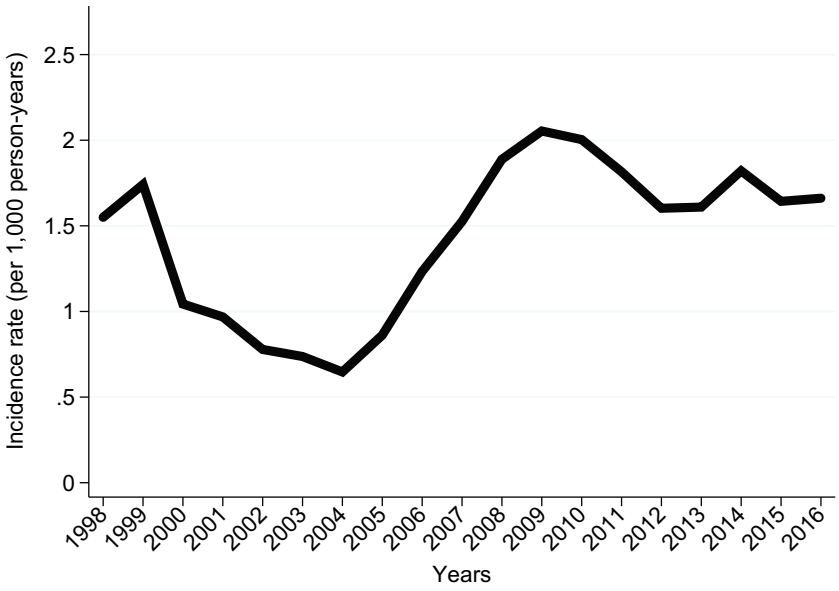

Fig. 4 Standardised incidence rates of montelukast from 1998 to 2016

Another explanation could be the extension of therapeutic indications. However, according to the FDA regulatory history of montelukast, subsequent indications involving the paediatric population were all approved in the USA before 2003 (included prophylaxis of asthma attacks in 2 to 5 years of age, treatment of asthma in 12 months and older, relief of symptoms of seasonal allergic rhinitis in adults and paediatric patients 2 years of age and older). Relief of symptoms of perennial allergic rhinitis in adults and paediatric patients 6 months or older was added to montelukast's therapeutic indications in 2005, thus could have affected the increase in paediatric prevalence proportions after 2005 [28]. Unfortunately, the regulatory history of montelukast in the EU is not easily available as montelukast was granted marketing authorisation in decentralised procedures. But it is much likely that the regulatory history of montelukast in the USA and Europe has followed the same timeline.

Notably, 11% filled a prescription of SABA or SAMA or combinations alone, or with an addition of nasal topical anti-allergic treatment and/or systemic antihistamines. According to the GINA criteria, this corresponds to step 1 [1]. The reason for initiating montelukast before initiating ICS or ICS + LABA among these individuals is unclear, some possible explanations could be (1) in individuals suffering from intermittent and/or exercise-induced asthma, (2) in individuals experiencing side-effects to inhalation therapy and (3) in an attempt to increase adherence.

According to the approved therapeutic indications, montelukast can also provide symptomatic relief of seasonal allergic rhinitis, and is indicated in the prophylaxis of asthma

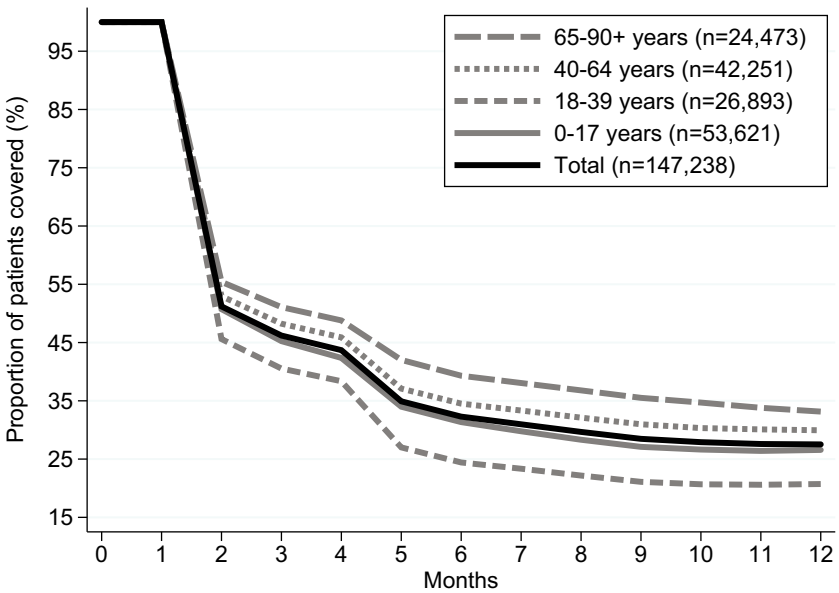

Fig. 5 Duration of montelukast therapy according to age groups

Table 2 Number of persons filling a prescription of either short-acting inhalation therapy, long-acting inhalation therapy, nasal topical treatment or systemic antihistamines up to a year prior to montelukast initiation

	All	Age 0–17 years	Age 18–39 years	Age 40–64 years	Age 65–90+ years
Total	(*n* = 147,247)	(*n* = 53,621)	(*n* = 26,893)	(*n* = 42,252)	(*n* = 24,481)
SA[a] only	11,382 (7.7%)	7165 (13.4%)	1353 (5.0%)	1518 (3.6%)	1346 (5.5%)
LA only	14,761 (10.0%)	3666 (6.8%)	2394 (8.9%)	4808 (11.4%)	3893 (15.9%)
LABA[b]	1347 (0.9%)	134 (0.2%)	199 (0.7%)	455 (1.1%)	559 (2.3%)
LAMA[b]	266 (0.2%)	1 (0.0%)	5 (0.0%)	67 (0.2%)	193 (0.8%)
ICS[b]	30,884 (21.0%)	18,994 (35.4%)	2807 (10.4%)	4740 (11.2%)	4343 (17.7%)
LABA + ICS[b]	26,012 (17.7%)	4369 (8.1%)	5361 (19.9%)	10,121 (24.0%)	6161 (25.2%)
LAMA + ICS[b]	274 (0.2%)	1 (0.0%)	10 (0.0%)	96 (0.2%)	167 (0.7%)
LABA + LAMA[b]	94 (0.1%)	0 (0.0%)	1 (0.0%)	32 (0.1%)	61 (0.2%)
LABA + LAMA + ICS[b]	2568 (1.7%)	5 (0.0%)	61 (0.2%)	943 (2.2%)	1559 (6.4%)
Nasal topical only	6085 (4.1%)	1465 (2.7%)	1467 (5.5%)	2321 (5.5%)	832 (3.4%)
SAH only	6461 (4.4%)	1586 (3.0%)	1895 (7.0%)	2218 (5.2%)	762 (3.1%)
Combinations					
SA[a] and LA[b] only	46,684 (31.7%)	19,838 (37.0%)	6050 (22.5%)	11,646 (27.6%)	9150 (37.4%)
SA[a] and nasal topical only	1203 (0.8%)	377 (0.7%)	301 (1.1%)	350 (0.8%)	175 (0.7%)
SA[a] and SAH only	1969 (1.3%)	758 (1.4%)	479 (1.8%)	502 (1.2%)	230 (0.9%)
SA[a], nasal topical, and SAH only	1488 (1.0%)	397 (0.7%)	550 (2.0%)	457 (1.1%)	84 (0.3%)
LA[b] and nasal topical only	4053 (2.8%)	621 (1.2%)	837 (3.1%)	1813 (4.3%)	782 (3.2%)
LA[b] and SAH only	3317 (2.3%)	738 (1.4%)	726 (2.7%)	1210 (2.9%)	643 (2.6%)
LA[b], nasal topical, and SAH[b] only	3581 (2.4%)	695 (1.3%)	995 (3.7%)	1433 (3.4%)	458 (1.9%)
Nasal topical and SAH only	6412 (4.4%)	1632 (3.0%)	2021 (7.5%)	2206 (5.2%)	553 (2.3%)
SA[a], LA[b], and nasal topical only	8734 (5.9%)	2138 (4.0%)	1872 (7.0%)	3351 (7.9%)	1373 (5.6%)
SA[a], LA[b], and SAH only	9560 (6.5%)	3100 (5.8%)	1895 (7.0%)	3034 (7.2%)	1531 (6.3%)
SA[a], LA[b], nasal topical, and SAH	8009 (5.4%)	2156 (4.0%)	2126 (7.9%)	2901 (6.9%)	826 (3.4%)
Nasal topical or SAH or a combination	18,958 (12.9%)	4683 (8.7%)	5383 (20.0%)	6745 (16.0%)	2147 (8.8%)
No LABA, LAMA, ICS, SABA, SAMA, SAH or nasal topical	1148 (0.8%)	34 (0.1%)	279 (1.0%)	440 (1.0%)	395 (1.6%)

SABA short-acting beta-2-agonists; SAMA short-acting muscarinic agonists; LABA long-acting beta-2-agonists; LAMA long-acting muscarinic agonists; ICS inhaled corticosteroids; SAH systemic antihistamines; Nasal topical Nasal topical anti-allergic treatment

[a] Short-acting inhalation therapy (SABA, SAMA and combinations)

[b] LA long-acting (LABA, LAMA, ICS and combinations)

in which the predominant component is exercise-induced bronchoconstriction. We found that 13% all individuals initiating montelukast filled a prescription of nasal topical anti-allergic treatment or systemic antihistamines, or a combination, but did not fill prescriptions of inhalation therapy.

An American study of 2082 patients in a managed care organisation in Upstate New York initiating montelukast treatment from 2001 to 2002 found that 61% did not have an ICS claim in their profile 1 year prior to the index date [5]. This number is substantially higher than that in our current study. The reason for this discrepancy could be differences in patient populations. The American study used a managed care organisation, more prone to selection bias than our nationwide setting.

Several studies have shown modest benefit of montelukast in diseases like eosinophilic oesophagitis [29], for the treatment of capsular contraction in patients undergoing breast enlargement [30], for stable COPD with eosinophilic bronchitis [9], for secondary prevention of cardiovascular disease [31], nasal polyposis [6] or allergic bronchopulmonary aspergillosis [7]. Further, case studies have shown benefit in reducing blood eosinophilia [27], and perhaps also on the treatment of cystic fibrosis [32].

Conclusions

The usage of montelukast has increased over threefold since it was marketed in 1998, mainly driven by the increased number of prevalent users. The incidence rate over time showed a bimodal curve, with a maximum point in 2009. The majority of individuals who initiated montelukast filled a prescription

of SABA up to a year prior to montelukast initiation, whereas almost half filled prescription of ICS, leaving only 0.8% that seemingly used montelukast off label.

Compliance with ethical standards The study was approved by the Danish Data Protection Agency. According to Danish law, pure register studies do not require approval from an ethics review board [24].

Conflict of interest AP reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Servier and Leo Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper.

DPH, JRD, CBL, AC, JH and PD declare no conflicts of interest.

References

1. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2017. Available from: http://www.ginasthma.org/
2. Singh RK, Tandon R, Dastidar SG, Ray A (2013) A review on leukotrienes and their receptors with reference to asthma. J Asthma 50:922–931
3. Joos S, Miksch A, Szecsenyi J, Wieseler B, Grouven U, Kaiser T et al (2008) Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review. Thorax 63:453–462
4. Medicines and Healthcare products Regulatory Agency (MHRA) Montelukast SmPC [Internet]. [cited 2017 Jan 16] Available from: http://www.mhra.gov.uk/spc-pil/?subsName=MONTELUKAST&pageID=SecondLevel
5. Lakomski PG, Chitre M (2004) Evaluation of the utilization patterns of leukotriene modifiers in a large managed care health plan. J Manag Care Pharm 10:115–121
6. Rix I, Håkansson K, Larsen CG, Frendø M, von Buchwald C (2015) Management of chronic rhinosinusitis with nasal polyps and coexisting asthma: a systematic review. Am J Rhinol Allergy 29:193–201
7. Morice AH, Kastelik JA, Aziz I (2001) Montelukast sodium in cystic fibrosis. Thorax 56:244–245
8. Walton SM, Schumock GT, Lee K-V, Alexander GC, Meltzer D, Stafford RS (2008) Prioritizing future research on off-label prescribing: results of a quantitative evaluation. Pharmacotherapy 28:1443–1452
9. Celik P, Sakar A, Havlucu Y, Yuksel H, Turkdogan P, Yorgancioglu A (2005) Short-term effects of montelukast in stable patients with moderate to severe COPD. Respir Med 99:444–450
10. Davidsen JR, Søndergaard J, Hallas J, Siersted HC, Lykkegaard J, Andersen M (2010) Increased use of inhaled corticosteroids among young Danish adult asthmatics: an observational study. Respir Med 104:1817–1824
11. Phillips C, McDonald T (2008) Trends in medication use for asthma among children. Curr Opin Allergy Clin Immunol 8:232–237
12. Cohen S, Taitz J, Jaffe A (2007) Paediatric prescribing of asthma drugs in the UK: are we sticking to the guideline? Arch Dis Child 92:847–849
13. Casares-Alonso I, Cano-Garcinuño A, Blanco-Quirós A, Pérez-García I (2015) Anti-asthmatic prescription variability in children according to age. Allergol Immunopathol (Madr) 43:383–391
14. Bollinger ME, Diette GB, Chang C-L, Stephenson JJ, Sajjan SG, Fan T et al (2010) Patient characteristics and prescription fill patterns for allergic rhinitis medications, with a focus on montelukast, in a commercially insured population. Clin Ther 32:1093–1102
15. Soh JY, Ng B, Tan Z, Xu S, Hing WC, Wu TS, et al. (2014) Ten-year prescription trends of asthma medications in the management of childhood wheeze. Allergy Asthma Proc. [Internet]. OceanSide Publications, Inc; [cited 2017 Jan 17]. e1–8. Available from: http://www.ingentaconnect.com/content/ocean/aap/2014/00000035/00000001/art00002
16. Hallas J, Støvring H (2006) Templates for analysis of individual-level prescription data. Basic Clin Pharmacol Toxicol 98:260–265
17. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M (2016) Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol
18. Lynge E, Sandegaard JL, Rebolj M (2011) The Danish National Patient Register. Scand J Public Health 39:30–33
19. Schmidt M, Pedersen L, Sørensen HT (2014) The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 29:541–549
20. WHO Collaborating Centre for Drug Statistics Methodology (2013) Guidelines for ATC classification and DDD assignment 2013 [Internet]. Oslo, Norway. Available from: http://www.whocc.no/filearchive/publications/1_2013guidelines.pdf
21. Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J (1980) Can simple clinical measurements detect patient noncompliance? Hypertens 2:757–764 Dallas Tex 1979
22. Pottegård A, Broe A, Hallas J, de Muckadell OBS, Lassen AT, Lødrup AB (2016) Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study. Ther Adv Gastroenterol 9:671–678
23. Hallas J, Støvring H, Pottegård A (2016) Individual level drug utilization analyses. Drug Util. Res. Methods Appl. Chichester: Hoboken: John Wiley & Sons Inc
24. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H (2011) Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health. 39:12–16
25. Schmidt M, Hallas J, Laursen M, Friis S (2016) Data Resource Profile: Danish online drug use statistics (MEDSTAT). Int J Epidemiol 45:1401–142g
26. Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology. Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review [Internet]. FDA; 2012 p 40. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM414065.pdf
27. National Center for Biotechnology Information, U.S. National Library of Medicine, PubMed. Pubmed Search: (montelukast OR "leukotriene receptor antagonist") AND (paediatric OR pediatric OR child OR children). https://www.ncbi.nlm.nih.gov/pubmed/?term=(montelukast+OR+%22leukotriene+receptor+antagonist%22)+AND+(paediatric+OR+pediatric+OR+child+OR+children)
28. FDA Briefing Document, Nonprescription Drugs Advisory Committee Meeting. Risk/Benefit Considerations for Use of Montelukast as an OTC Allergy Symptom Reliever. 2014
29. Kumar M, Sweis R, Wong T (2014) Eosinophilic oesophagitis: investigations and management. Postgrad Med J 90:273–281
30. Huang CK, Handel N (2010) Effects of Singulair (montelukast) treatment for capsular contracture. Aesthet Surg J 30:404–408
31. Ingelsson E, Yin L, Bäck M (2012) Nationwide cohort study of the leukotriene receptor antagonist montelukast and incident or recurrent cardiovascular disease. J Allergy Clin Immunol 129:702–707 e2
32. Schmitt-Grohé S, Zielen S (2005) Leukotriene receptor antagonists in children with cystic fibrosis lung disease: anti-inflammatory and clinical effects. Paediatr Drugs 7:353–363