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ORIGINAL REPORT

Representativeness of diabetes patients participating in a web-based adverse drug reaction monitoring system

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ABSTRACT

Purpose Lareb Intensive Monitoring, LIM, is a non-interventional observational cohort method which follows first-time users of certain drugs during a certain period of time and collects information about adverse drug reactions, ADRs. In order for LIM to be a useful pharmacovigilance tool, it is important to know whether the LIM population is comparable to the whole population using the drug.

The aim of this study is to compare the LIM diabetes population with an external diabetes reference population on characteristics that may influence the patient's susceptibility for ADRs.

Methods In this study, a LIM diabetes population was compared to a reference diabetes population derived from The Groningen Initiative to ANalyse Type 2 diabetes Treatment project. Comparisons were made regarding age, gender, body mass index and polypharmacy, as well as diabetes medication used and disease/treatment duration.

Results LIM patients were more often men (58.5% vs 50.8%) and in general younger (59.1 vs 64.7 years) and healthier, by that meaning they had a higher percentage of de novo treated patients (55.5% vs 53.2%), a shorter diabetes treatment duration (3.7 vs 5.5 years) and used less co-medication than patients in the reference population.

Conclusions This study shows that diabetes patients participating in a web-based intensive monitoring system differ from a reference population. The observed differences might lead to an underestimation of ADRs, but it is not clear whether this would also influence the type or time-course of the reported ADRs. When interpreting results from LIM studies, one should take these differences into account.

KEY WORDS—pharmacovigilance; adverse drug reaction; intensive monitoring; web; diabetes population; pharmacoepidemiology

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INTRODUCTION

In the Netherlands, the national pharmacovigilance centre Lareb, which is responsible for maintaining the spontaneous reporting system, has developed a web-based intensive monitoring system called Lareb Intensive Monitoring (LIM). LIM is a monitoring system which prospectively follow cohorts of first-time users of specific drugs, identified through the first dispensing signal in community pharmacy, for a certain period of time using longitudinal data collection through web-based questionnaires. The LIM methodology has been described in more detail elsewhere.[1,2]

For a new pharmacovigilance system such as LIM to be a useful tool, it is important to know whether the population who chooses to participate in LIM is comparable to the population using the drug. Otherwise, it might be difficult to extrapolate the results to the population at large. The participation rate in previous studies has been around 5% of all the patients receiving a first dispensing for a specific drug.[2,3]

In 2008, a LIM cohort study was started monitoring the safety of all anti-diabetic drugs used to treat diabetes mellitus type 2 except the insulins. The aim of this study is to compare the LIM diabetes population with an external diabetes reference population on characteristics that may influence a patient's susceptibility for an adverse drug reaction (ADR).

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METHOD

LIM diabetes population

A LIM diabetes patient was defined as a person who, in the period between February 1, 2008 and November 1, 2011, received a first dispensing of a new oral anti-diabetic drug or a glucagon-like peptide-1 (GLP-1) analogue which the patient had not used in the previous 12 months and registered for the LIM study. Only anti-diabetic drugs which were registered before February 1, 2008 were included during the study period. In the LIM population, demographic information (gender, birth date, height, weight), information relating to the study including date of entering the study, study drug use and concomitant drug use (type of drugs as well as start date and if applicable stop date) were asked. In addition, information about ADRs and an open question about previous use of anti-diabetic drugs were collected through structured questionnaires. The questionnaires were filled in at registration, and at 2 and 6 weeks and 3, 6, 9 and 12 months after starting the anti-diabetic drug. All data, except for previous use of anti-diabetic drugs, were collected in the registration questionnaire.

Reference population

The Groningen Initiative to ANalyse Type 2 diabetes Treatment (GIANTT) database is a registry of ambulant patients with type 2 diabetes mellitus in the northern part of the Netherlands.[4] It contains demographic information (birth date, gender, date of first registration and end of registration and date of death), prescriptions, symptoms and diagnoses as recorded in text or with the International Classification of Primary Care, medical history, results of physical examination expressed as numerical data and laboratory results of patients with type 2 diabetes as documented in electronic primary care medical records.[5] Before the GIANTT database was chosen as a reference database, the GIANTT population was compared to the population in other Dutch diabetes databases to make sure it was a suitable reference population.[6]

A GIANTT reference patient was defined as a person who received a first prescription of an oral anti-diabetic drug or a GLP-1 analogue in the period between January 1, 2008 and November 1, 2011. A first prescription was defined as 'an oral anti-diabetic drug prescription or a GLP-analogue without a prescription for the same drug in the 12 months prior to the date of prescription'.

Data extraction in the LIM population

The age of the LIM patients was calculated in years from the date of birth to the start date of the first prescription in the study period. The body mass index (BMI) was calculated using weight and height. Values smaller than 10 and greater than 50 were considered to be invalid and were excluded from further analysis. Patients were considered to be de novo anti-diabetic drug users when they did not report any co-medication belonging to the group of anti-diabetic drugs (Anatomic Therapeutic Class (ATC) code A10) and reported that they had not used any anti-diabetic drugs in the past. The patients who reported an anti-diabetic drug as co-medication provided information about the start year which was used to calculate the diabetes treatment duration. If more anti-diabetic drugs were used, the oldest start date was used. The start date of any previously used anti-diabetic drugs, however, was not available. For patients who did not provide a start date for their anti-diabetic drugs, no duration could be calculated, and these patients were omitted from the analysis about treatment duration. The number of concomitantly used drugs was restricted to drugs commonly used for chronic diseases, i.e. belonging to the ATC chapters A (Alimentary tract and metabolism), B (Blood and blood forming organs), C (Cardiovascular system), H (Systemic hormonal preparations), L (Anti-neoplastic and Immunomodulated agents), M (Musculo-skeletal system, N (Nervous system) and R (Respiratory system).

Data extraction in the reference population

The age of patients in the reference population was calculated from the date of birth to the date of the first prescription in the study period. The BMI value available from the medical records which was closest in time to the first prescription was used. To calculate the diabetes treatment duration, the date of the first prescription of an anti-diabetic drug ever and the date of first prescription in the inclusion period for this cohort were used. In the reference population, the patient would be seen as de novo if the date of the first prescription of any anti-diabetic drug was the same as the date of the first prescription for inclusion in this cohort. The number of concomitantly used drugs, using the same ATC restrictions as above, was based on the drugs prescribed in a period up to 120 days prior to the first prescription of the oral anti-diabetic drug. This period was chosen since chronic drugs are commonly prescribed for a period of 3 months in the Netherlands.

Analysis

In the LIM population as well as in the reference population a patient could be included more than once depending on how many first prescriptions of an anti-

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diabetic drug the patient received during the study period. For the comparison between the drugs of the first prescription, all first prescriptions were included.

The anti-diabetic drugs on which the patient entered the study were divided into four groups: biguanides, sulphonylurea derivates, GLP-1 analogues or dipeptidyl peptidase 4 (DPP-4) inhibitors, and the remaining group of other oral anti-diabetic drugs. If the patient started on a combination drug, the patient was registered in the group as described above to which the newest substance in the combination belonged. For comparing the populations at first prescription regarding gender and age distribution, BMI, disease/treatment duration, de novo anti-diabetic drug use and number of drugs used as co-medication, a patient was included only once, using the values from the first prescription during the study period. Differences in demographic and clinical characteristics between the two populations were tested with Chi-2 and Fisher exact tests for categorical data and with two-tailed t-tests for normally distributed data and Mann–Whitney U-tests for skewed data. The comparisons of gender and co-medication in the two populations were stratified by age groups in 5-year intervals, since age could be a confounder in the results of the comparisons. The odds ratio of being female in the LIM population compared to the reference population was calculated using logistic regression and stratified by age groups. MS Access 2000 was used for LIM data retrieval. Statistical analyses were performed using SPSS for Windows version 17.0. *P*-values below 0.05 were considered statistically significant.

RESULTS

In the study period, 2828 patients were included in the LIM population, and 11,852 patients were included in the reference population. The LIM population included more males, was on average more than 5 years younger, and used on average less co-medication in comparison to the reference population (Table 1). Furthermore, it included around 55% de novo diabetes treatment patients, which was slightly more than the 53% observed in the reference population. The treatment duration of those already on treatment was almost 4 years, which was more than a year shorter as compared to the reference population. The frequency order of the drugs included as a first prescription was similar between LIM and the reference population with biguanides being the most frequently initiated drug (almost 60%) followed by sulphonylurea derivates (around 25%). In the LIM population, the GLP-1 analogues and DPP-4 inhibitors were slightly more included (Table 1).

The analysis for the comparison of being female in the two populations stratified by age groups shows that in the younger age categories (under 45) there were more females in LIM compared to the reference population, between the ages of 45 and 59 the gender distribution was almost equal and in the age categories above 60, the reference population contained more females, see Figure 1.

In LIM the number of co-medication commonly used for chronic conditions was relative stable around 2–3 drugs, regardless of age. In the reference population, the number of co-medication increased by age, see Figure 2.

Table 1. The comparison of the LIM diabetes population with a reference population. The number of patients or the mean with standard deviation or the median with the inter quartile range are presented

	LIM		***GIANTT***		
	n	*n with % or mean with SD or median with IQR*	*n*	*n with % or mean with SD or median with IQR*	P
Gender	2828		11 852		<0.0001
Men		1653 (58.5%)		6020 (50.8%)	
Women		1175 (41.5%)		5832 (49.2%)	
Age (years)	2828	59.1 (± 10.7)	11 852	64.7 (± 12.7)	<0.0001
BMI (kg/m2)	465	29.66 (± 5.3)	6740	30.76 (± 5.6)	<0.0001
De novo anti-diabetic drug users	1570	55.5%	6310	53.2%	<0.0001
Unclassified	273	9.7%	-	-	
Duration diabetes treatment (years)	985	3.7 (1.3–6.9)	5542	5.5 (3.3–8.9)	<0.0001
Number of co-medication	2828	2.0 (1–4)	11 852	4.0 (2–7)	<0.0001
Total number of first prescription	2890		15 320		<0.0001
-Biguanides		1721 (59.6%)		8744 (57.1%)	
-Sulphonamides, urea derivatives		707 (24.5%)		4492 (29.3%)	
-DPP-4 inhibitors and GLP-1 analogues		329 (11.4%)		1257 (8.2%)	
- Remaining group		133 (4.6%)		827 (5.4%)	

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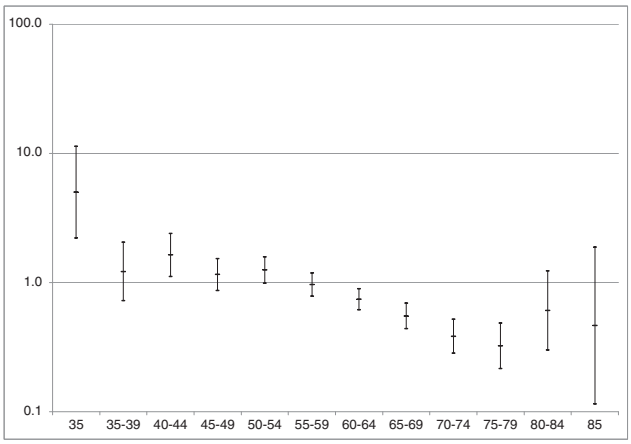

Figure 1. Gender stratified by age-class (in years) shown as odds ratios, where the odds ratio was calculated as female/male ratio in LIM compared to the reference population

DISCUSSION

Principal findings

The two populations were compared on parameters which might influence a patient's susceptibility to develop an ADR, such as age,[7,8] gender,[9] BMI[10,11] and polypharmacy at the time when a new anti-diabetic drug was started.[12] LIM patients were in general younger and healthier, by that meaning that they were more often de novo anti-diabetic drug users, had a diabetes treatment duration and used less co-medication than patients in the reference population. In contrast to the reference population, co-medication did not increase for patients in the LIM population with increasing age. Furthermore, the LIM population included relatively more females in the youngest age categories and more males in the elderly categories as compared to the reference population.

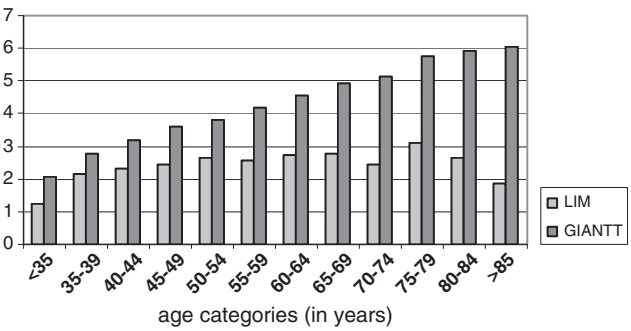

Figure 2. Mean number of co-medication per age class (in years)

The *age difference* between the two groups of more than 5 years could be attributed to internet access and computer skills. Older patients may have less access to and knowledge or trust about internet. These patients would therefore not register with the LIM diabetes study. In addition, older patients may have an impaired cognitive function, which might not make LIM participation possible. It has been found that higher age or other factors closely linked to age, for example comorbidity and co-medication, are associated with an increased susceptibility for ADRs.[8,13] This would imply that LIM is likely to underestimate ADRs. It is not clear, however, whether the type of ADRs experienced or reported will be affected by age, but it has been suggested that type A ADRs are more common in the elderly and the unpredictable type B ('bizarre' or idiosyncratic reactions) less common.[14]

The LIM database contains slightly more men than women. When gender is corrected for age, there are no differences in distribution between the ages of 45 and 59. Above 65 years, the reference population contained more females which might be due to the fact that older men are more familiar with using computers and internet compared to older women. Studies have shown that women are more prone to develop ADRs than men.[8] The mechanisms behind these differences are not known. There are several factors that have been suggested to play a role, including pharmacokinetic and pharmacodynamic factors, hormonal influences, health-care utilisation, reporting bias and increased use of drugs in women. The pharmacokinetic differences such as higher plasma drug levels and a higher percentage of body fat in women may result in females experiencing more dose-related effects.[9] A LIM study where more men are participating than women would probably lead to an underestimation of ADRs.

The *diabetes treatment duration* in LIM is shorter than in the reference population. The LIM population is younger than the reference population, and if one assumes that the age of diabetes onset is the same in the two populations, this might explain the difference in diabetes treatment duration.

The number of *co-medication* in the reference population is higher than in the LIM population. In the reference population, the number of co-medication increases with age, and this trend is not seen in LIM where the number of co-medication stays quite constant between the different age groups. As we know, the number of co-medication increases with age,[15,16] the fact that this is not seen in the LIM population could be due to a healthier LIM population with respect to age and diabetes. The number of de novo patients is also slightly larger in LIM than the

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reference population, and one can assume that these are healthier than chronic patients and will thus use less co-medication.

The pattern of the drugs used for the first prescription is similar between LIM and the reference population and mirrors the guideline for diabetes treatment in the Netherlands.[17] In LIM, the GLP-1 analogues and DPP-4 inhibitors were slightly more included as compared to the reference population. Maybe, pharmacists are more active in recruiting patients who use these drugs because they are new chemical entities and knowledge about their ADRs is scarce.

Limitations

In this study, we compare a web-based intensive monitoring population with a reference population to see whether these two populations are comparable. Ideally, one would like to compare the LIM diabetes population with the patients who are LIM non-responders, but since this information is not readily available, it was chosen to compare the LIM population with a reference population consisting of patients with diabetes.

By comparing the LIM diabetes population with a reference population, data of different origin and kind are used. In both systems, data can be missing. For example, BMI data were very incomplete, limiting the value of its comparison. The reference population is based on medical records, and LIM is based on direct information from the patients and the data in both data sets were not collected with the aim of comparing the two data sets with each other. Therefore, not all the parameters that were needed for the comparison were readily available; some parameters could only be obtained by proxy or when certain assumptions were made.

Some of the differences found in this study could partly be due to way the data were collected or extracted. Specifically, this might have played a role regarding the diabetes treatment duration and co-medication data. In the reference population, the duration was calculated using the date of the first prescription ever of an anti-diabetic drug. In LIM, the date of the first dispensing ever was not known, and the date of the first dispensing of any anti-diabetic drug which the patient was using at the time of LIM registration was used to calculate the diabetes duration. If the patient had used other anti-diabetic drugs in the past but stopped using them before entering the study, these would not be taken into account when calculating the diabetes duration, yielding a shorter diabetes treatment duration than the actual diabetes treatment duration for the LIM population. On the other hand, also in the reference population, incomplete documentation of previously used drugs may occur. The number of co-medication in the reference population is based on the prescribed drugs instead of the used drugs, which means that an overestimation is possible in the reference population. In LIM, patients reported the drugs which they actually used; however, it is possible that LIM participants forgot or did not feel like to report all co-medication, giving an underestimation of the number of co-medication.

Finally, the differences found in this comparison are applicable to a cohort consisting of diabetes patients. LIM as a system is developed to monitor all kind of drugs, and it is not known to what extent the results of this study would be applicable for other populations. For example, limitations related to age, treatment duration or co-medication are likely to depend on the type of drug one is monitoring.

CONCLUSION

The aim of this study was to test whether a web-based intensive monitoring population differs from a reference population concerning parameters that might influence a patient's susceptibility to develop an ADR. This study shows that diabetes patients participating in a web-based intensive monitoring system are more often men and in general younger and possibly healthier than the reference population. Such differences might lead to an underestimation of ADRs, but it is not clear whether this would also influence the type or time-course information of ADRs reported. Differences found in this study have to be taking into account when interpreting results from web-based intensive monitoring studies.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest.

KEY POINTS

- A web-based intensive monitoring diabetes population differs from a reference population. Patients participating in a web-based intensive monitoring system are more often men and in general younger and possibly healthier than the reference population.
- The differences detected might lead to an underestimation of adverse drug reactions, but it is not clear whether this would also influence the type or time course of ADRs reported.

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