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Quality and completeness of utilisation data on biological agents across European countries: tumour necrosis factor alpha inhibitors as a case study

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ABSTRACT

Purpose: For optimal decision making on access to and regulations around biologicals availability of national utilisation data is a prerequisite. This study characterises the main categories of critical issues in collecting available national utilisation data on tumour necrosis factor alpha (TNFalpha) inhibitors in different European countries.

Methods: Data were collected on characteristics of the nature of TNFalpha usage data and on usage of TNFalpha itself (2003–2007). Utilisation rates were expressed as defined daily doses (DDDs)/1000 inhabitants/day. Data from Denmark, Finland, Ireland, the Netherlands, Norway and Portugal were included.

Results: Characteristics of TNFalpha (usage settings and ways of distribution to patients) and databases (type of data collected, public availability and data sources) influenced the way data were collected and determined the type of research and policy questions that can validly be addressed. The prevailing differences in the structure of national databases are prohibitive for critical aspects of medicines utilisation studies. An increase in TNFalpha usage over time was observed in all countries and varied widely from 0.32 (Portugal) to 1.89 (Norway) DDDs/1000 inhabitants/day (2007).

Conclusions: In the European countries studied data on national TNFalpha usage is not easily, if at all accessible. Intercountry collaboration and sharing of technical resources will facilitate harmonisation of data collection allowing independent, population based, health and outcomes research.

INTRODUCTION

Modern biotechnology agents, such as tumour necrosis factor alpha (TNFalpha) inhibitors, significantly altered the treatment paradigm of rheumatoid arthritis (RA) therapy from treating to preventing symptoms.^{1, 2} Biologicals are now being prescribed earlier and more often as combination therapy than

they were 5 years ago.^{2, 3} Also new indications (i.e. psoriasis plaques, M. Crohn) for these agents have been approved opening additional therapeutic windows.⁴

A number of independent academia-initiated but industry sponsored medicines registers have been set up by several national rheumatology societies in European countries to monitor their long-term safety and effectiveness and to make sure that benefits from clinical trials are confirmed in clinical practice.^{5–7}

With the exception of RA registers in e.g. Denmark and Sweden, most biologics registers are not-population based and catchment areas are not always known.^{5, 7–9} Besides, biologics registers exist in only a limited number of countries for a limited number of diseases and medicines. Even if the catchment area is known, the data can not be easily extrapolated to cover the whole population. An Australian study has shown that access to anti-rheumatic biologicals varied considerably among different regions.¹⁰ The utilisation roughly correlated with the per capita ratio of rheumatologists. Other factors like patient's income, indirect costs and cultural beliefs also influenced the use of specialist care. Geographic variation in access to biologicals has also been identified in the United Kingdom (post-code prescribing)¹¹ whereas a recent study conducted in the US showed geographic variation in Medicare pharmaceutical spending in general.¹² Prospects of people diagnosed with RA seem to be substantially influenced by geographical location.¹³

For governments, regulators or policy analysts, who have to decide on what medicines should remain/be subsidised, who should have access, what restrictions should apply to access and what a reasonable distribution would be between reimbursement and the individual contribution, data covering the whole population are essential and should be easily available. Affordability of and access to these types of medicines are becoming increasingly problematic for healthcare systems and individuals, as healthcare resources are finite and innovative biological medicines are very expensive.¹⁴ Consequently it is vital that in individual countries, a system designed to collect data about the actual and total consumption of these medicines is in place, either by a medical records or an administrative database.^{15, 16}

So far no other studies have assessed the methodological difficulties in collecting and analysing (publicly) available national utilisation data for biologicals. Studies have looked at problems in collecting comparable data for small molecules in Europe using different types of databases to obtain the full picture of medicines consumption.^{17–19} Although these studies provided valuable information, additional issues may be encountered when collecting usage data for biologicals, because of the nature of these medicines (e.g. various distribution ways, intravenous or subcutaneous administration).

Therefore, the aim of this study was to identify and assess in terms of policy implications, the methodological problems one encounters when collecting national usage data on biologicals in a sample of different European countries using TNFalpha inhibitors as an example.

METHODS

TNFalpha inhibitors

In Europe until 2008, three TNFalpha inhibitors, infliximab (Remicade®), etanercept (Enbrel®) and adalimumab (Humira®), had been approved by the Committee for Medicinal Products for Human Use (CHMP).^{1, 20–22} Although not all TNFalpha inhibitors were initially approved for RA, by 2007 all three TNFalpha inhibitors have had several approved indication extensions including RA, see Table 1. All of these TNFalpha inhibitors were included in the present study.

[TABLE 1]

Data collection

Data collection was realised with support of the European PILs (Post-Innovation Learning Cycle for Pharmaceuticals) network, an international research network involved in the study of the effects of pharmaceutical policies in medicines use.²³ Eleven countries were approached to participate in this study. Finally, six European countries were included in this study providing a balanced sample in terms of heterogeneity of health-care and pharmacy systems, reimbursement rules and availability of usage data. These countries included Denmark, Finland, Ireland, the Netherlands, Norway and Portugal.

Two different types of data were collected for this study, i.e. questionnaire data on specific characteristics related to the availability of TNFalpha inhibitors usage data as such and quantitative utilisation data.

Questionnaire data

Information was collected on the following determinants that could influence the way data was collected on TNFalpha inhibitors utilisation: public availability of the databases, type of data collected, usage setting of the TNFalpha inhibitors and means of distribution to patients.

Utilisation data

Table 2 shows an overview of the sources used for the extraction of the utilisation data. The anatomical therapeutic chemical (ATC)/defined daily dose (DDD) methodology was chosen as method for presenting drug utilisation data.²⁴ The DDD is a dosage measure determined by the World Health Organisation and is based on the assumed average daily maintenance dose for its main indication use in adults.^{18, 24} Utilisation data were obtained for products with ATC codes L04AB01 (etanercept), L04AB02 (infliximab) and L04AB04 (adalimumab) and covered the period 2003–2007. For infliximab, the DDD is 3.75 mg, for etanercept 7 mg and for adalimumab 2.9 mg.^{25, 26} DDDs used in this study are the DDDs for the main indication (RA) and resemble the usual dose for RA as reflected in the current national guidelines (e.g. the DDD of etanercept is 7 mg and the usual dose for RA is 50 mg weekly).^{27–31} The data, available on a yearly basis, were obtained from ambulatory, hospital or total care. The data were presented on an aggregate level in DDDs/year or in DDDs/1000 inhabitants/day.²⁵ In order to achieve collection of consistent and comparable data, the country representative of each participating country was required to provide the data by means of a specially developed and standardised questionnaire.

[TABLE 2]

Data analysis

Utilisation rates (DDDs/1000 inhabitants/day) were calculated using the mid-year number of persons covered by a data source, or the mid-year population of a country according to the national statistics agency. For the Netherlands, inpatient data were only available for the years 2006–2008 whereas outpatient data were available for the period 2003–2008. Since the ratio between the in- and outpatient use for 2006–2008 was relative constant (1.65, range 1.59–1.69), this ratio was also used to calculate the missing inpatient use for the years 2003–2005.

RESULTS

Various factors influenced the ease of data collection. Some factors were specifically related to the way TNFalpha inhibitors are used in clinical setting, other factors were related to the way data are available and collected.

Factors related to TNFalpha inhibitor usage

Due to the intravenous/subcutaneous administration routes and for monitoring of adverse events, treatment with TNFalpha inhibitors is initiated by a specialist, mainly operating in hospitals. If patients are well-instructed and able to self-administer these medicines, treatment may be continued at the patient's home. Portugal is the only country in which the use of TNFalpha inhibitors is limited to hospitals only (until 2007). In the other countries, outpatient dispensing is an exclusive task of community pharmacies, except for the Netherlands where outpatient distribution of etanercept and adalimumab is realised via two channels; pharmacies and specialised distributions centres. These distributions centres receive the orders through the Internet and deliver the products by mail or courier service.^{32, 33}

The various ways in which TNFalpha inhibitors are distributed affect the capturing of national utilisation data. Dispensing, and/or wholesales data should be able to cover usage from either inpatient or outpatient but sales data from wholesalers to community pharmacies in general will not cover hospital data. Claims data will be most likely to include data from both settings. Due to the specific distribution systems in the Netherlands, data from a third delivery route should be covered by the database as well. Depending on the source (claims, wholesales or dispensing data) these data will or will not be included.

Factors related to the databases

(Public) availability of the databases

Finland, Denmark and Norway provided national utilisation data available in the public domain. To capture utilisation data from Ireland and Portugal collaboration with country representatives was necessary. Both representatives had unrestricted access to outpatient TNFalpha utilisation data. Hospital sales data for these countries were provided through their contracts with IMS Health. TNFalpha inhibitor utilisation for the Netherlands was captured using a public (outpatient) and a non-publicly (in- and outpatient data) available database. The latter did not cover the full study period. Both sources captured usage distributed by the unique deliveries.

Data collection – type and setting

Only Finland, Denmark and Norway included data from both the in- and outpatient setting within one source. In the Netherlands one database did capture both data from the in- and outpatient setting but another database was required to obtain total national utilisation over the full study period. The data used in this study all come from administrative databases, who generally record information as a by-product of financial transactions. In Ireland and the Netherlands, the databases involved captured different types of data, outpatient data were captured by claims data whereas inpatient data were captured by sales data. To capture medicines utilisation in the four remaining countries, sales data were used in both Portugal and Denmark, whereas wholesale data were used in Finland and Norway. All data sources covered more than 98% of the total population. No database was able to give information on patient characteristics (age, gender and/or diagnosis) or off-label use. All data could be converted into one common unit of measurement (DDDs/1000 inhabitants/day).

Utilisation data

Large variations over time were observed in overall utilisation (Figure 1). For the year 2007, utilisation of all TNFalpha inhibitors varied strongly and ranged from 0.32 DDDs/1000 inh/day for Portugal to 1.89 DDDs/1000 inh/day for Norway. An increase in use over time could be demonstrated for all countries.

Figure 1. Trend over time of TNFalpha inhibitors usage defined in Defined Daily Dose/1000 inhabitants/day. *Inpatient data 2003–2005 based on ratio between in- and outpatient data in 2006–2008. Therefore, 2003–2005 represent estimated (inpatient) and actual data (outpatient)

[FIGURE 1]

Consequences for pharmacoepidemiological and policy research

The specific characteristics of TNFalpha inhibitors influence the kind of databases available for data collection and consequently (co)determine the type of research questions that can validly be addressed. Table 3 reflects the situation in which databases, capable of collecting national utilisation data on biologicals may or may not be suitable. This table shows that data collection is more complicated with respect to data on biologicals. Pharmacoepidemiological studies are feasible as based on these data but only at an aggregated level. The databases are generally less detailed in their clinical contents but yet are often representative and complete while covering large patient populations including elderly patients, children and those in nursing homes, all of them being most often underrepresented in or totally excluded from clinical trials. Within the field of pharmaceutical policy research these data are valuable and can help provide answers to new public health questions as they can be linked to relevant system characteristics such as guidelines and reimbursement restrictions or country characteristics such as pharmaceutical expenditures and gross domestic product.

[TABLE 3]

DISCUSSION

The main purpose of the present study was to set out critical methodological issues related to the collection of TNFalpha inhibitor usage data in various European countries. Critical issues that were encountered were the (public) availability, the type of data collected and the specific distribution routes and clinical setting in which TNFalpha inhibitors are used. Although some of these are generally known for all kind of data collections for pharmaceutical policy and regulatory purposes, this study shows that acquiring

insight in the usage of biologicals seems to be a particular challenge. When no single comprehensive database exists, national usage data can only be collected by using multiple sources like dispensing, wholesale and claims data. The specific characteristics related to the TNFalpha inhibitors such as direct delivery of TNFalpha inhibitors to patients, and both in- and outpatient utilisation complicate data collection further as different databases are (sometimes) required to obtain the complete picture of actual consumption. In the present study, more than one database was required to capture national TNFalpha utilisation, in four out of the six countries. In this relation, the Netherlands probably provide a key example of complexity of the various delivery routes of TNFalpha inhibitors. Distribution can be organised through hospitals, pharmacies and/or specialised distribution centres. Portugal provides an example of a country that has an effective system in place that collects usage data for the outpatient setting. Nevertheless, data collection becomes complicated when it concerns medicines used in the inpatient setting. In all situations more standardisation of data collection would be helpful to improve comprehensive national collection of utilisation data, to enable cross-country comparison and to avoid an over-/underestimation or double counting of the actual consumption. Some databases cover the whole population; others use a sample to collect utilisation data, and then extrapolate these data to cover the entire population. This is normally seen as valid for estimates of prevalence or incidence. Double counting or extrapolation corrections are constant factors within a database and will not influence the trend over time of TNFalpha utilisation as shown.

The (public) availability of the data is also a critical element. Availability may differ from restricted access (data as property of a specific institution/organisation) to unrestricted access (data available in the public domain), with or without payment. This study showed that public availability increases the ease of data collection not necessarily leading to inferior quality of the data; the public available databases of the Nordic countries included data on the number of people treated with immunomodulating agents although it was unknown for which indication, which specific agent and whether they were counted double when using multiple immunomodulating agents. For databases, like IMS, data on the hospital sector is not always available. This is in part because data for some countries is based on only a sample, which might lead to over- or underestimation or because the distribution system is complicated which troubles data collection (e.g. the Netherlands). For policy makers involved in making decisions such as for evaluating the clinical and economic effects of medicines reimbursement policy changes, in countries where a national register is lacking or without contracts with commercial databases, public available databases are important.

Another factor that may hamper the interpretation of our data is the fact that we sampled European countries on the basis of the willingness of selected key national officials to participate, availability of usage data and heterogeneity of health-care system processing prescriptions and dispenses of TNFalpha inhibitors. Reasons for not participating were (i) non-response to the questionnaire sent ($n = 3$), (ii) national medicines utilisation monitoring systems were not (yet) operational as the finance method of the TNFalpha inhibitors changed during the last 10 years. Inpatient data could sometimes not be provided as the costs (when values are transformed to volumes) of TNFalpha inhibitors used in hospitals were subsumed into the overall hospital budget rather than being specifically identifiable or within a specific budget ($n = 1$) and (iii) non-availability of data was considered a political sensitive issue, therefore data could not be given to third parties ($n = 1$). Although these factors may have induced some selection bias, we believe that the primary aim of the study, i.e. to identify and assess in terms of policy implications the methodological problems one encounters when collecting national usage data on TNFalpha inhibitors has not been jeopardised. The array of identified methodological challenges for utilisation research on such a clinically relevant drug class is in our view comprehensive and valid.

The methods we used to quantify the utilisation data may have some limitations as well. The DDD methodology was chosen as it enables comparison of use within the category as well as it enables time comparison of the changing patterns across different countries when data on a patient level is not available. However, the DDD methodology should be handled with caution when recommended dosages differ from one indication to another and where the prescribed daily dose (PDD) may differ from one population to another (e.g. according to sex, age, ethnicity or geographic location). For infliximab, the concept of DDDs has important limitations as the dose is weight-based, differs between indications and dose-escalations are frequent, as are changes of the infusion interval. For this study, however, we assumed that these differences would occur in all studied countries and would therefore not influence the trend as seen. But when the assessment of reliable utilisation rates is the main goal of a study, this should be taken into account.

The volume of TNFalpha inhibitors consumed varied substantially between the different European countries studied. The highest usage was reported for Norway and the lowest amount of usage reported for Portugal. An increase in use over time was reported for all countries. Further studies should be conducted to reflect on the differences in usage seen between countries and take different indications into account.

In conclusion, this study shows that current data capture methods for TNFalpha inhibitors usage are heavily influenced by the practice of health-care and pharmacy systems delivering these products to patient care. This study emphasises the need for more coordination between (local) registers in order to enhance the collection of comparable national utilisation data. Ideally patient registers would cover the *whole* population. However using the current data with their acknowledged limitations gives a rather quantitative indication of usage not available by any other means. It also provides insights into the trend in consumption of these agents. Improved intercountry collaboration and related sharing of technical resources will facilitate the harmonisation of data collection efforts and the development of a standard methodology will help to improve international data on medicines consumption allowing not only useful health-care planning but also independent, population based, health and outcomes research.^{34–36}

KEY POINTS

This is the first study investigating the quality and completeness of data collection on a national level for biologicals.

Our findings indicate that data collection is more complicated with respect to data on biologicals and innovative methods of data capture for biologicals may be required in some countries. This consequently (co)determine the type of research questions that can validly be addressed.

Using the current data with their acknowledged limitations gives a rather quantitative indication of usage not available by any other means. It also provides insights into the trend in consumption of these agents. We believe that this study will contribute to scaling up optimal decision and policy making on access to and regulations around biologicals.

This study emphasises the need for more coordination between (local) registers in order to simplify the collection of comparable national utilisation data. Improved intercountry collaboration and related sharing of technical resources will facilitate the harmonisation of data collection efforts and the development of a standard methodology will help to improve international data on medicines consumption allowing not only useful health-care planning but also independent, population based, health and outcomes research.

CONFLICT OF INTEREST

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Table 1. Initial approval indications and approved indication extensions for infliximab, etanercept and adalimumab

Indication approved by EMA	Date of issue of marketing authorisation by EMA		
	Infliximab	Etanercept	Adalimumab
Crohn's disease	13 August 1999	–	4 June 2007
Rheumatoid arthritis	27 June 2000	10 May 2004	8 September 2003
Ankylosing spondylitis	15 May 2003	16 January 2004	1 June 2006
Psoriatic arthritis	24 September 2004	5 December 2002	1 August 2005
Plaque psoriasis	29 September 2005	24 September 2004	19 December 2007
Ulcerative colitis	28 February 2006	–	–
Juvenile idiopathic arthritis	–	3 February 2000	25 August 2008

EMA, European Medicines Agency.

Table 2. Data sources (as used in 2009)

Country	Data source	Data type	Hospital data included?	% of inpatient use for 2007	Coverage population (%)	Years covered
Denmark	DKMA	Sales	Yes	±100%	100	2003–2007
Finland	NAM	Wholesaler	Yes	44%	100	2003–2007
Ireland	HSE	Claim	No		100	2003–2007
	IMS Health	Sales	Yes	8%	100	2003–2007
The Netherlands	GIP	Claim	No	Not available	100	2003–2007
	Farminform	Sales	Yes		>98	2006–2008
Norway	Norwegian Institute of Public Health	Wholesaler	Yes	Not available	100	2003–2007
Portugal	CEFAR	Dispensing	No*		100	NA*
	IMS Health	Sales	Yes	100%	100	2003–2007

DKMA, Danish Medicines Agency; NAM, National Agency for Medicines; HSE, Health Service Executive; IMS, Intercontinental Marketing Services; GIP, Drug Information Project; CEFAR, Centre for Health Studies and Evaluation; NA, not applicable.

*Until 2007, use of TNFalpha inhibitors is restricted to hospitals.

Figure 1. Trend over time of TNFalpha inhibitors usage defined in Defined Daily Dose/1000 inhabitants/day. Inpatient data 2003–2005 based on ratio between in- and outpatient data in 2006–2008. Therefore, 2003–2005 represent estimated (inpatient) and actual data (outpatient)

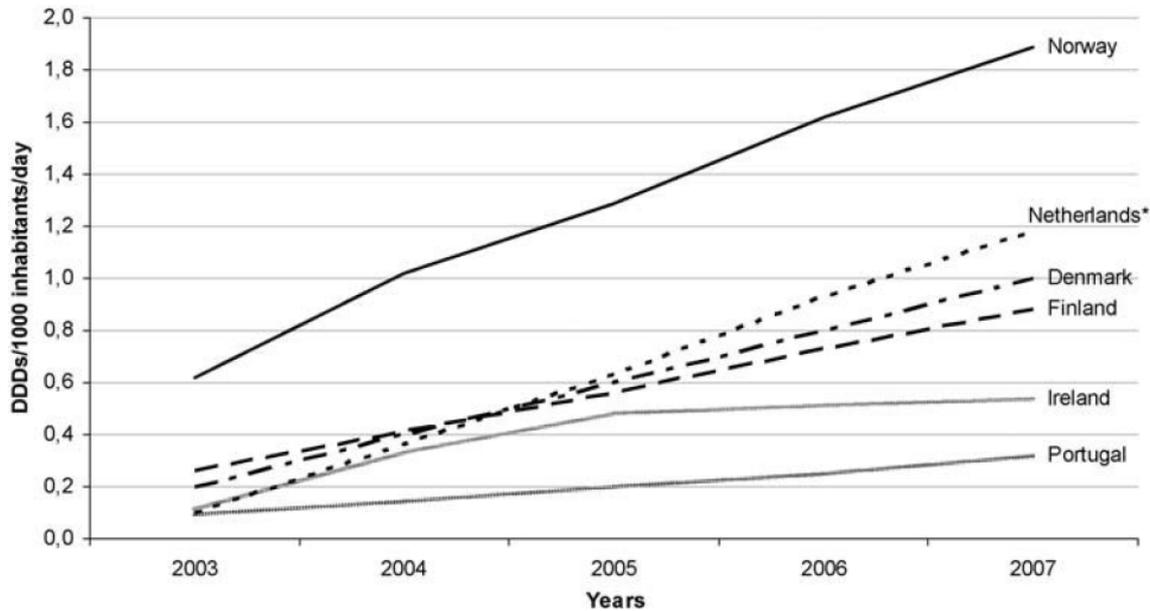


Table 3. Possibilities and limitations of biological usage data on medicines utilisation studies

Possibilities	Effect of biologicals
<ul style="list-style-type: none"> To link system (such as reimbursement regulations) and cultural characteristics to medicines utilisation To link medicines utilisation to country related factors, like Gross Domestic Product and pharmaceutical expenditures To study time trends in medicines consumption on a national level 	<p>More complicated as several databases are required</p> <p>More complicated as several databases are required</p> <p>More complicated. Not all countries are able to collect this kind of data on a national level or for the same time period</p> <p>More complicated as less countries are able to provide data</p>
<ul style="list-style-type: none"> To study time trends in medicines consumption between countries 	<p>More complicated as less countries are able to provide data</p>
<p>Limitations</p> <ul style="list-style-type: none"> Adjust for potential important confounders such as smoking status, alcohol use and body mass index. To study medicines consumption for specific indications To perform a cross sectional analysis (observation at a defined time) 	<p>More complicated due to data type</p> <p>More complicated due to data type</p> <p>More complicated because of multiple types of data and multiple data sources (error around time point will influence observation)</p>