ACCESS TO INNOVATIVE TREATMENTS IN RHEUMATOID ARTHRITIS IN EUROPE

OCTOBER 2009

A REPORT PREPARED FOR THE EUROPEAN FEDERATION OF PHARMACEUTICAL INDUSTRY ASSOCIATIONS (EFPIA)

Gisela Kobelt, PhD MBA
Department of Orthopedics, Lund University (Sweden)
European Health Economics (France)
Gisela.Kobelt@he-europe.com

Frida Kasteng, MSc
i3 Innovus, Stockholm (Sweden)
Frida.Kasteng@i3innovus.com

EUROPEAN HEALTH ECONOMICS

LUNDS UNIVERSITET

i3 innovus

CONTENT

	Introduction	i-ii
1	Burden of RA in Europe	1:1 – 1:15
2	Cost of RA in Europe	2:1 – 2:13
3	Uptake of Biologic Treatments in RA	3:1 – 3:19
4	Determinants of Access to Treatment in RA	4:1 – 4:18
5	The Value of Treatment in RA	5:1 – 5:16

Introduction

A recent series of publications investigated the burden of rheumatoid arthritis (RA) and the access to biologic treatments during the first years of their availability in Europe and a number of non-European countries [1]. The current work is a continuation of the earlier study, with the objective to present new data and expand the discussion on issues regarding access, costs and value created by biologic treatments.

Few areas in health care have seen medical progress such as RA. The first significant relief for patients came with the introduction of cortisone in the 1950s, followed by the use of methotrexate in the early 1990's. Outcome was further improved with the increased use of disease modifying anti-rheumatic drugs (DMARDs) earlier and earlier in the disease process with the goal to slow the disease process. The largest breakthrough came with the introduction of the TNF-inhibitors in the late 1990s and their ability to not only effectively control inflammation but prevent or slow the development of irreversible joint erosion.

As truly disease-modifying agents, these biological agents should ideally be used as early as possible in the course of the disease, to avoid the development of permanent functional limitations associated with dependence for daily activities and frequently loss of work capacity. The continuous research into the disease, the introduction of new classes of biologic drugs, and the treatment effects achieved have further highlighted the need and the benefits of early intervention. Treatment guidelines by scientific societies in many European countries focus on enhancing rapid diagnosis and early treatment with the most effective agents for patients with active and potentially erosive disease.

However, the side-effect profile of the new biologic treatments has led to a cautious initial use, essentially in patients with severe active disease despite best treatment at the time. Many countries have established special registries to follow safety issues for these treatments. These registries also include measures of effectiveness, thereby opening the possibility to investigate outcome in the medium and longer term. With time and large amounts of safety data available, treatment initiation has occurred earlier, in patients at lower levels of disease activity and functional disability and shorter duration of the disease.

Widespread use of biologic drugs has also been hampered by their cost. At introduction, they faced reimbursement and usage restrictions in most European countries, generally through limitations in the number of patients eligible for treatment. Patients had to have highly active disease despite treatment with two to three DMARDs, including methotrexate. These restrictions – be it by reimbursement mechanisms or treatment guidelines - differ between countries, explaining part of the differences in usage patterns of biologic drugs illustrated in the earlier report [1]. Other differences stem from price differences, the access to specialists, the level of insurance, the cost (price) in relation to countries' wealth, and it is difficult to single out any of these factors as the major cause.

Earlier intervention will increase the number of patients eligible to treatment. The duration of biologic's use will increase with the introduction of further biologic drugs, enlarging the choice of treatments and enabling their use in sequence. Cost for biologics will thus increase and with it the focus on their cost-effectiveness. Economic evaluations in RA have been performed over two decades, evolving from the analyses

of short-term clinical trials to the development and acceptance of sophisticated modeling studies spanning 10 or more years all the way to life-time. Indeed, in chronic progressive diseases, the full benefit, both in clinical and economic terms, of treatments that modify the course of the disease is only evident over time, as fewer patients progress to severe disease associated with high social costs and low quality of life.

Early modeling studies of biologics show different results for a number of reasons, the most important being the underlying data, the country of study and the perspective adopted. All models incorporate a number of assumptions, but the paucity of data is more pronounced in some countries and some studies. More importantly, however, reimbursement or health technology assessment agencies in few countries take a societal perspective. In this perspective, all costs regardless of who incurs them – the health care system, the patient, society as a whole – are taken into consideration. In the case of RA, as for other chronic progressive diseases, it appears difficult to argue that costs outside the health care system should not be considered in the decision making process. Production losses due to temporary and permanent loss of work capacity and the dependency on informal help are a major, if not the largest, part of total costs of the disease.

Models predicted high but acceptable cost effectiveness ratios for the biologics when used in the right patient populations, but full verification of these estimates still eludes us. It takes many years to observe the full outcome, and a number of issues make such analyses difficult. The first patients treated for whom a number of years of follow-up are available were the most severe cases with substantial irreversible disease consequences in terms of functional handicap and loss of work capacity. Currently, at least in Western Europe, most patients who are eligible for treatment are on treatment, and no comparator group from clinical practice is available. However, a wealth of clinical observations is available regarding the short and medium term benefit. Part of these observations can be related to economic outcomes and provide insight into the value of investing into these treatments.

In this report on access to treatment in 30 European countries (27 EU member states plus Iceland, Norway and Switzerland) as well as Turkey, we will address

1) The burden of the disease in terms of epidemiology and the effect on quality of life
2) The cost of the disease in Europe, using a predictive cost model and updated epidemiological and economic data
3) The uptake over time of biologic treatment and the number of patients treated, using available sales data from IMS, adjusted where necessary and possible
4) The conditions and hurdles that affect usage and differences between countries
5) Current knowledge on the value of these treatments, with a focus on parameters that have an economic effect.

with the objective to provide material for discussion of how to fully utilize the opportunities created by medical research and innovation.

1. *Jönsson B, Kobelt G, Smolen J. The burden of rheumatoid arthritis and access to treatment: uptake of new therapies. Eur J Health Econ 2008;8 (Suppl 2):S33-106.*

Chapter 1 - Burden of Rheumatoid Arthritis

We gratefully acknowledge the contribution of

- Marta Pentek MD PhD (Corvinus University, Budapest, Hungary) for support with literature search and with the Hungarian data.
- Martin Engelund, PhD, (MORSE project, University of Lund) for the data from Southern Sweden.
- Lennart Jacobsson, MD PhD (University of Lund, Sweden) with general advice on prevalence data.

CONTENTS

1.1 Summary 1:1
1.2 Prevalence of RA 1:2
1.2.1 Literature review 1:2
1.2.1.1 Timing 1:2
1.2.1.2 Samples and Reporting 1:3
1.2.1.3 North-South Gradient 1:4
1.2.2 Estimation of Prevalence 1:4
1.2.3 Comparison to Published Data 1:11
1.3 Health Burden 1:12
1.3.1 DALYs in RA 1:12
1.3.2 QALYs in RA 1:13
1.4 Conclusions 1:15
1.5 References 1:15

TABLES

Table 1-1- Prevalence Estimates based on 1987 ACR Criteria 1:3
Table 1-2 – Prevalence rates used for the calculations (%/adult population) 1:5
Table 1-3 – Prevalence rates and estimated number of patients (>19) 1:7
Table 1-4 - Total Estimated Number of Patients (Europe 30 plus Turkey) 1:11
Table 1-5 – Comparison of Estimates to Published Data 1:11
Table 1-6 – Utilities in different chronic diseases. 1:13

FIGURES

Figure 1-1 – Age structures in the different countries (>19) 1:6
Figure 1-2 – Estimated Prevalence 1:8
Figure 1-3 – Estimated number of patients 1:9
Figure 1-4- Estimated proportions of patients in different age groups 1:10
Figure 1-5 – The share of morbidity and mortality in the disease burden 1:12
Figure 1-6 – Utility related to disease severity 1:14
Figure 1-7 – Rating of disease symptoms 1:14

1 Burden of Rheumatoid Arthritis

1.1 Summary

In this chapter we define the burden of Rheumatoid Arthritis (RA) as the burden for people living with the disease resulting from reduced health (reduced quality of life) and for Society from the number of people affected (prevalence). The economic burden will be discussed in the next chapter.

The literature gives conflicting data on the prevalence of RA, with numbers varying up to ten-fold. This represents a difficulty when estimating and comparing the proportion of the patient population on treatment with innovative treatments in different countries. We therefore propose a standardized way of estimating prevalence, based on 2 national datasets with patients by age and gender, with a definite diagnosis and follow-up for RA, i.e. more than one contact with the health care system. With this method, we estimate the prevalence in the European population >19 to be 0.49%, with a total number of patients in the EU 27 of slightly under 2 million.

The burden on patients - expressed as utility, a preference-based quality of life index anchored between 0=death and 1=full health - is one of the strongest (with low utilities) among chronic progressive diseases. The average utility has been estimate at around 0.5, but most importantly, in decreases from values closer to normal to very low values (0.1-0.2) as the disease progresses to severe health states with severe functional impairment.

1.2 Prevalence of RA

1.2.1 Literature review

The prevalence of RA has generally been estimated at 0.5-1.0% of the adult population [1], but range from 0.2 to 3.0% in published studies. A number of epidemiological reviews have focused on reporting results [2-5], but no attempt has been made to adjust and extrapolate the numbers to different countries.

It is thus difficult to directly derive an estimate of the number of prevalent patients in the different European countries. However, this is a prerequisite to estimating the total cost of RA in Europe, analyzing the uptake of the biologics and evaluating the proportion of patients on treatment. We therefore first discuss the issues related to the published literature and the difficulty to draw conclusions on the prevalence rates in the different countries, and then propose an approach to estimating European prevalence.

1.2.1.1 Timing

In 2002, Symmons and colleagues published a "new prevalence estimate for a new century" [6]. They demonstrate convincingly that prevalence in 1991-92 had decreased compared to 1981-82, by 31% in women and by 19% in men, essentially due to the 1987 revision of the criteria for classification of rheumatoid arthritis [7].

This trend is largely confirmed when analyzing the actual publication years of some of the studies included in the reviews. Although reporting in 1997, Abdel-Nasser and colleagues included essentially studies performed between 1968 and 1975 and all rates reported were around 0.9-1.1% of the adult population [2]. The findings from this review were also the primary source for data in the paper by Kvien in 1997 [3]. Subsequent reviews by Silman and Hochberg (Eds) [8] and Alamos and colleagues reported considerably lower rates [4, 5]. When excluding studies performed prior to 1990 from the review by Silman and Hochberg (Eds), rates range from 0.2-0.8%. Alamanos and colleagues conducted a review of studies published between 1988-2005, and found rates in Europe between 0.2-0.85% [5]. The majority of these studies were conducted between 1998 and 2002 and, not surprisingly, the authors found only limited trends for change over time [5].

Nevertheless it is possible that rates have declined somewhat further as the 1987 criteria are more widely used. Also, since the introduction of the biologic treatments and their restriction to a defined group of patients, much more focus is given to clear diagnoses, and the high number of "unspecified" cases may have largely disappeared.

Table 1-1- Prevalence Estimates based on 1987 ACR Criteria

Publication	Year	Country	Prevalence %	Population included
Hakala et al [9]	1993	Finland	0.8%*	>=16
Kvien et al [3]	1997	Norway	0.44*	20-79
Drosos et al [10]	1997	Greece	0.35	>=16
Cimmino et al [11]	1998	Italy	0.33*	>=16
Stojacovic et al [12]	1998	Yugoslavia	0.18*	>=20
Power et al [13]	1999	Ireland	0.50*	
Saraux et al [14]	1999	France	0.50	>=18
Simmonson et al [15]	1999	Sweden	0.51*	20-74
Riise et al [16]	2000	Norway	0.43*	>=20
Carmona et al [17]	2002	Spain	0.50*	>=20
Symmons et al [6]	2002	UK	0.85*	>=16
Andrianakos et al [18]	2003	Greece	0.70*	>=19
Guillemin et al [19]	2005	France	031	>=18
Akar et al [20]	2004	Turkey	0.36*	>=20
Laiho et al [21]	2001	Finland	1.8	>=65
Salaffi et al [22]	2005	Italy	0.46*	>=18
Hanova et al [23]	2006	Czech Rep	0.61*	>=16
Andrianakos et al [24]	2006	Greece	0.67	>=19
Roux et al [25]	2007	France	0.31	
Adomaviciute et al [26]	2008	Lithuania	0.55	>=18
Otsa et al[27]	2009	Estonia	0.46*	>=20

** crude rates*

Source: Adapted from Alamanos et al, Semin Arthritis Rheum 2006

** crude rates*

Additional studies, MedLine Update,(non-exhaustive)

1.2.1.2 Samples and Reporting

Published studies have included different populations or have been performed in different geographic areas within countries, and some findings were surprising. A recent study based on telephone interviews in two Lithuanian cities reported 0% prevalence in men and 1% in women, which is a rather unlikely result [26]. A French study found 32 cases but estimated prevalence rates in 7 different geographic areas [25]. Another study was performed in a female religious community. Two studies in Greece found rates of 3.5% [10] and 7% [24]. As illustrated in the table above, a majority also only report crude rates (i.e. not age adjusted).

Studies also included different age groups. While most cover the adult population above 16-18, some have not included patients above 80 (Norway) [3], while others only included people above 65 (Finland)[21]. For some studies it appears not entirely clear whether any limits were set. The men-to-women ratios reported are likely influenced by these difference in studies, but overall studies concur on a ratio of 1:2 to 1:3, but Symmons reported a higher proportion of men in the age-group 45 to 64 [6].

1.2.1.3 North-South Gradient

It is commonly accepted that prevalence is higher in Northern Europe than in Southern Europe, although it is difficult to understand where the separation line should be. Does a country like Germany belong to the North? If so, how should then France be classified, Northern or Mediterranean? In his first paper, Alamanos grouped countries into Northern and Southern Europe, but the split appears rather artificial [4]. The rate for Ireland is reported as 0.5%, while France has a rate of 0.6%. Yet France belongs to the South and Ireland to the North. Overall the ranges overlap and the North-South difference seems far from clear. In his second paper, Alamanos explores the difference further and comes to the conclusion that – while there seems to be a trend – the difference is not significant. Interestingly, a small French study found higher prevalence rates in Northern France than in Southern France [25], which could be due to a migration of retirees towards Southern France. Nevertheless, the data indicate that prevalence is somewhat higher in the Nordic area and the United Kingdom. This may be due to a number of reasons such as genetics, life style, climate and a long tradition of diagnosing and treating RA.

1.2.2 Estimation of Prevalence

These issues may not be a large issue when considering one country at a time. However, in this report, we build the estimate of the cost of RA in all European countries on three types of data: the mean cost per patient based on available cost analyses adjusted for economic factors, total sales of biologic drugs in each country, and prevalence. The latter is a crucial input, as it is used to estimate the proportion of patients treated in each country to estimate the mean drug cost per prevalent patient, and to extrapolate the mean cost per patient to total national and European costs.

In our previous paper [28] we based our estimates essentially on the first paper by Alamanos and used prevalence rates of 0.45% and 0.66% for Southern and Northern countries, respectively. However, in view of the issues discussed above, we now argue that prevalence might be rather similar across Europe, and that the considerable differences observed could be to some extent a consequence of

- the timing of the study (due to changes in diagnostic criteria and focus on rapid correct diagnosis)
- the region of observation (urban, rural; economic situation of the area)
- the study methods (design, sample, age adjustment)
- the age structure of a country (proportion of patients over 60)
- medical tradition and access to specialists for diagnosis.

We therefore propose a <u>different approach</u>, using the following arguments:

1. The variation in prevalence is in part due to the age structure, i.e. prevalence will be higher in countries with a larger population of elderly: Consequently, we used prevalence rates for 3 different age-groups: >19 to <45, 45 to 64, >64. The groups were chosen with a view to both the average age of diagnosis, workforce participation and mean salary.

2. The patient populations relevant for our calculations are those actually diagnosed, not the potential patient population including undiagnosed cases. These latter cases, although they cause costs to society, would not receive biologic treatments. We therefore used two official national datasets with confirmed numbers of diagnosed patients by age and gender to estimate the basic rate.

- For the Nordic area and the UK, detailed data from the administrative region of Southern Sweden (Skåne) were used (personal communication from Martin Englund, MORSE project, University of Lund, Sweden [29]) and combined with published data [6, 21]. The Skåne data included all patients with at least two contacts with the health care system for the diagnosis of RA.

- For continental and southern Europe, detailed data from official government statistics in Hungary (personal communication from Marta Pentek, Corvinus University, Budapest[30]) were combined with published data [17, 24, 26].

Overall prevalence in Sweden was 0.59% and in Hungary 0.49%. It was interesting to note that in the younger and middle age groups, rates in Sweden, Hungary and published data from other countries were almost identical. Differences related mostly to the age group over 65, with Sweden and the UK reporting higher rates than other countries. One might argue that this is a consequence of a long tradition of diagnosis, where patients diagnosed a long time ago now make up the patients over 65.

The table below indicates the rates used in our calculations by gender and age group. We used a cut-off of >19 years due to the way the data were available, but this should not have a major incidence on the total prevalence, considering the small number of cases below the age of 20.

These rates were then applied to the age structure of the individual countries and the number of prevalent patients estimated. The calculation also yielded an overall prevalence for each country which was then again compared to published data. However, for reasons of consistency, we did not make any further adjustments, but rather comment on the differences. A second verification was done against estimated numbers of patients provided by some of the companies marketing biologic drugs for RA. However, most of the numbers provided came from published literature, and had thus already been taken into account.

Table 1-2 – Prevalence rates used for the calculations (% per adult population)

Age groups / ***Countries***	***20 – 44***		***45 – 64***		***65 +***	
	Women	Men	Women	Men	Women	Men
Denmark, Finland, Iceland, Ireland, Norway, Sweden, UK	0.2	0.07	0.9	0.45	1.7	0.95
All other countries	0.17	0.07	0.8	0.4	1.3	0.65

Figure 1-1 – Age structures in the different countries (>19)

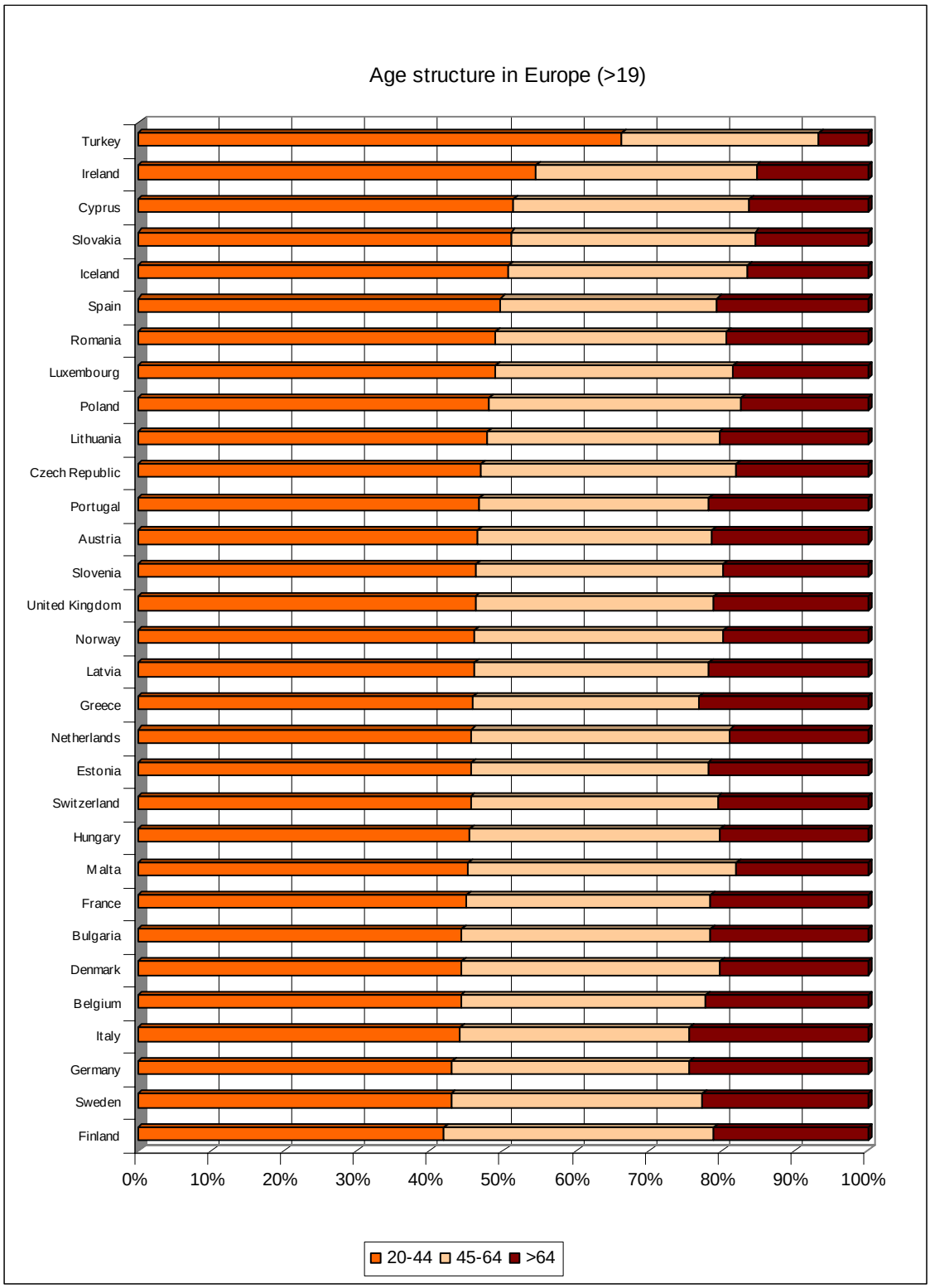


Table 1-3 – Prevalence rates and estimated number of patients (>19)

Country	Population >19 (000')	Patients >19	Prevalence >19 (%)
Austria	6,485	30,536	0.47
Belgium	8,113	39,209	0.48
Bulgaria	6,158	29,711	0.48
Cyprus	576	2,422	0.42
Czech Republic	8,126	37,037	0.46
Denmark	4,104	23,676	0.58
Estonia	1,038	5,124	0.49
Finland	4,039	24,279	0.60
France	47,375	226,750	0.48
Germany	66,032	328,844	0.50
Greece	8,960	42,574	0.48
Hungary	7,904	37,907	0.48
Iceland	212	1085	0.51
Ireland	3,099	15,035	0.49
Italy	47,717	235,898	0.49
Latvia	1,786	8,771	0.49
Lithuania	2,576	12,213	0.47
Luxembourg	358	1,589	0.44
Malta	309	1,419	0.46
Netherlands	12,380	56,934	0.46
Norway	3,451	19,486	0.56
Poland	29,207	131,546	0.45
Portugal	8,355	39,379	0.47
Romania	16,610	74,832	0.45
Slovakia	4,105	17,567	0.43
Slovenia	1,604	7,461	0.47
Spain	35,424	159,535	0.45
Sweden	6,916	41,576	0.60
Switzerland	5,852	27,469	0.47
United Kingdom	45,871	263,672	0.57
Turkey	44,823	137,905	0.31

The average prevalence for Europe (excluding Turkey) was estimated at 0.49%.

Figure 1-2 – Estimated Prevalence

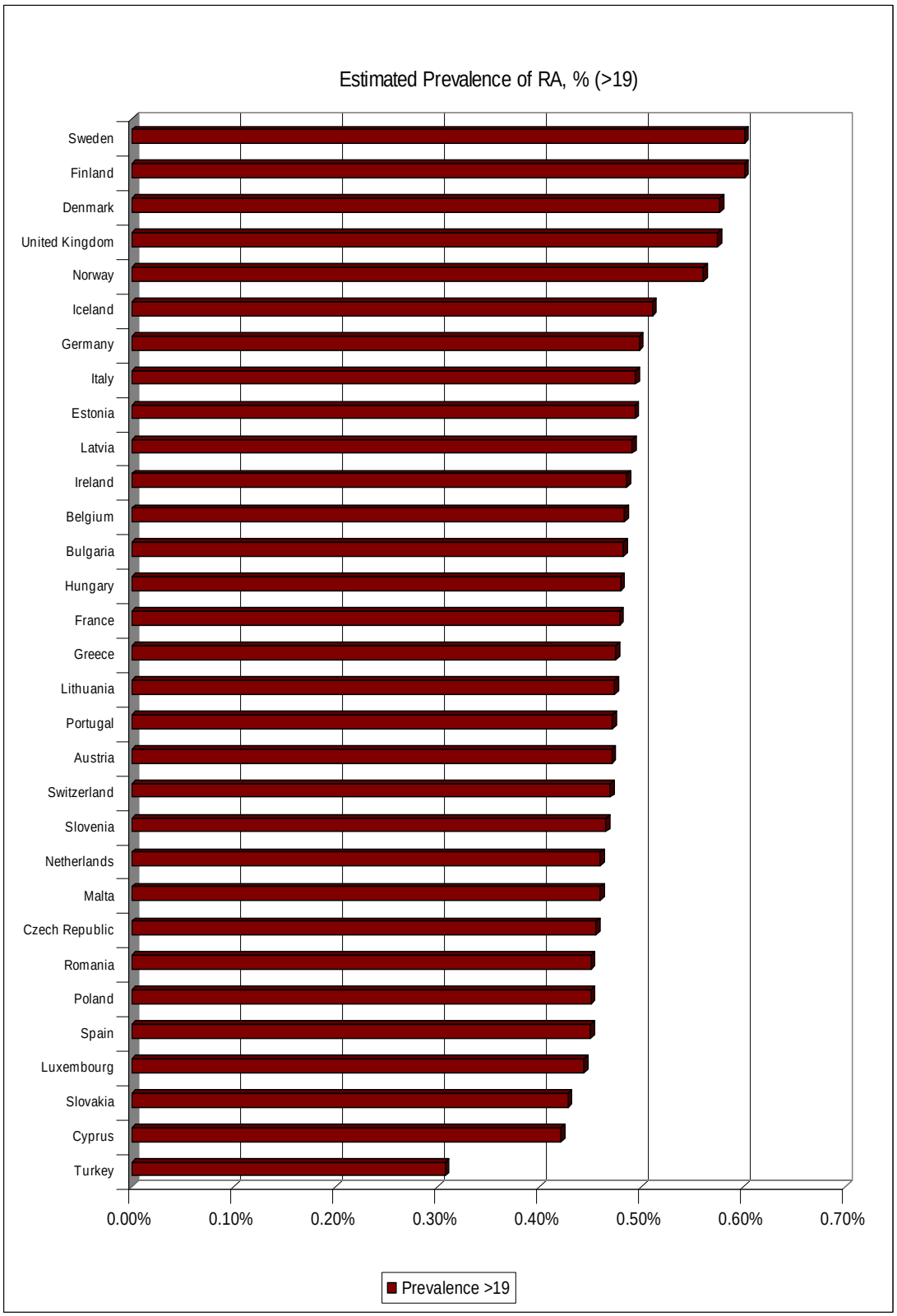


Figure 1-3 – Estimated number of patients

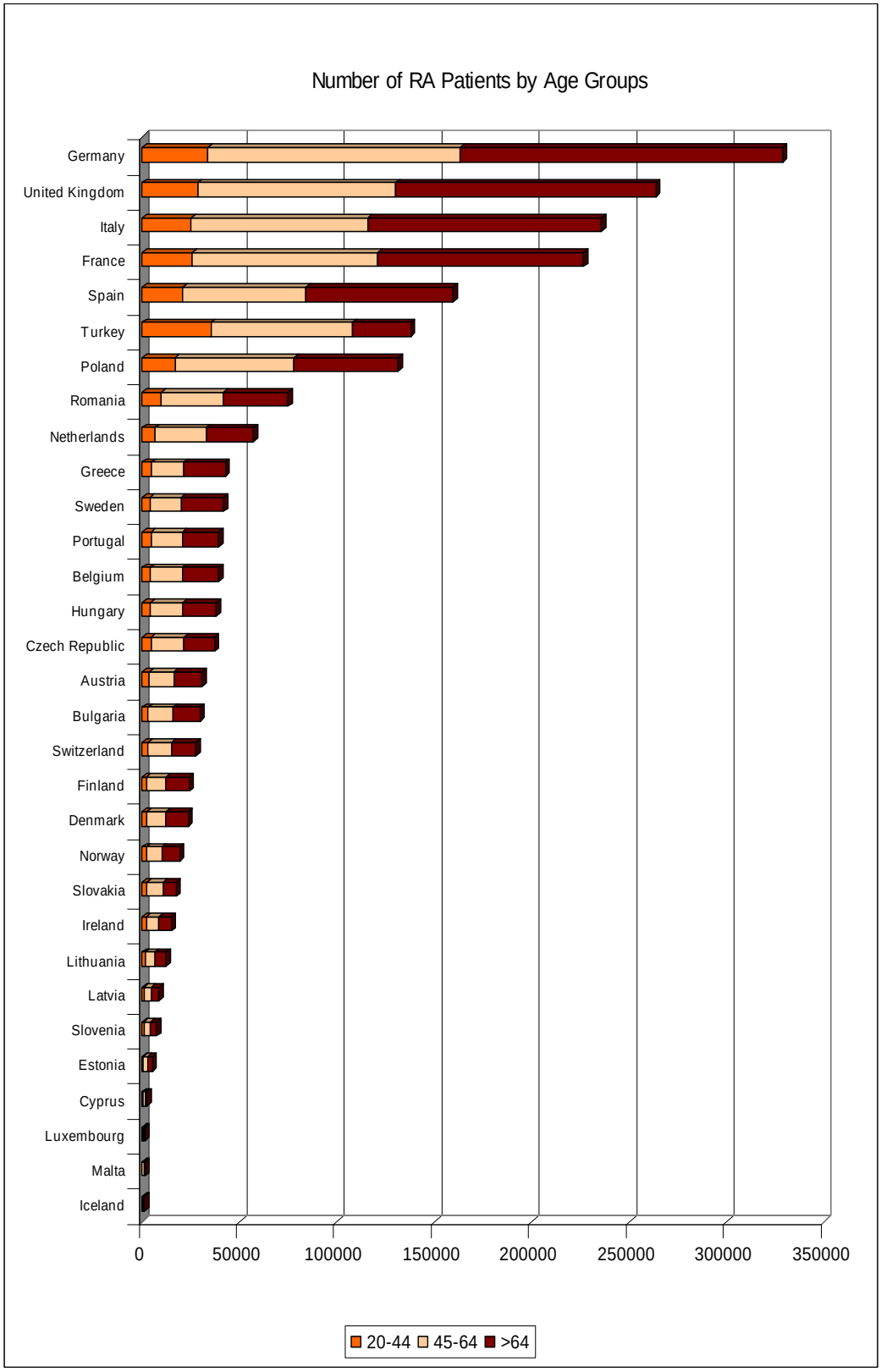
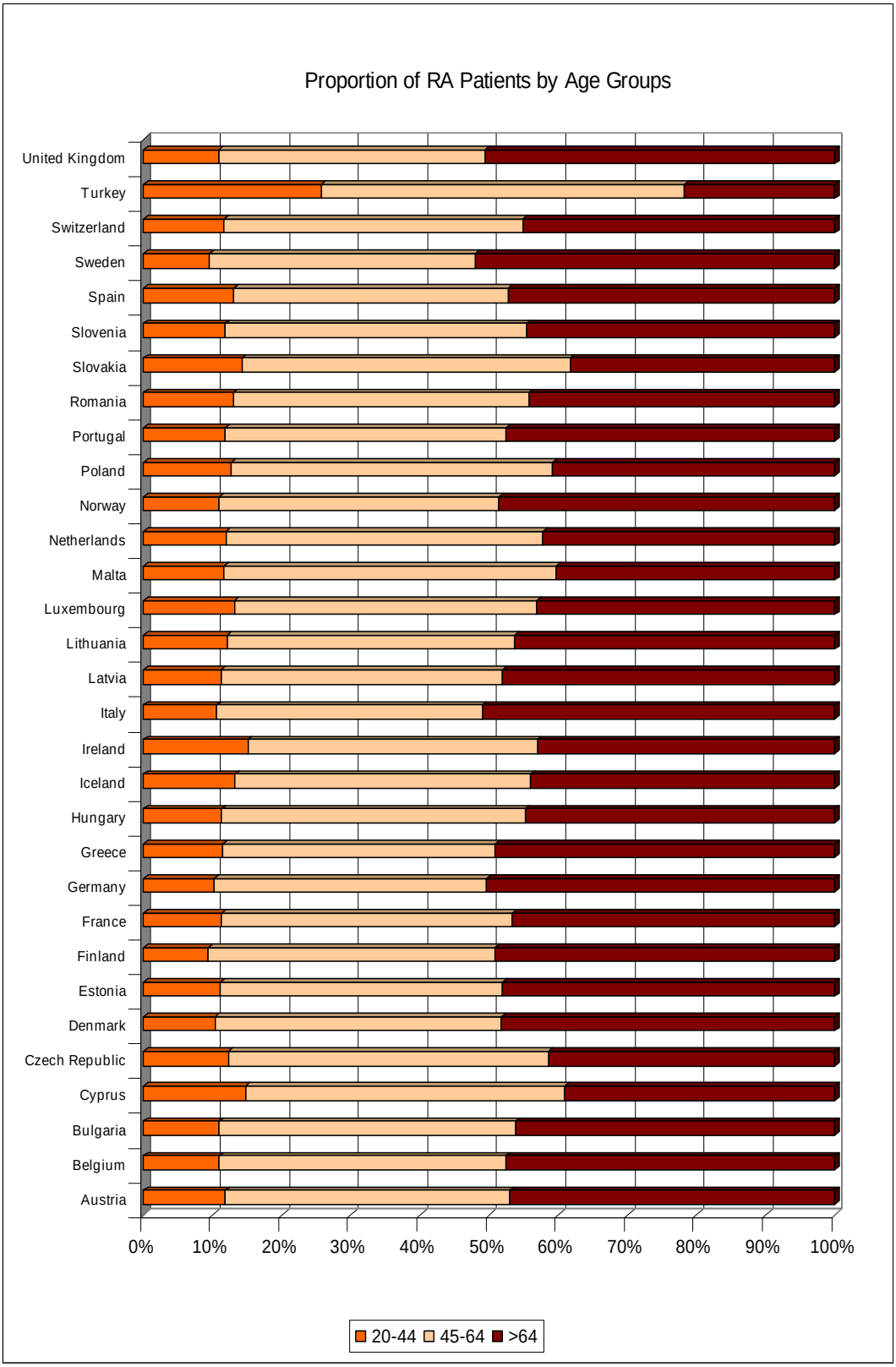


Figure 1-4- Estimated proportions of patients in different age groups



The total number of patients was estimated at close to 2 million for Europe, of which 1.6 million in Western Europe and 360,000 in Central/Eastern Europe (model output).

Table 1-4 - Total Estimated Number of Patients (Europe 30 plus Turkey)

	Women			Men			Total
	20-44	45-64	>64	20-44	45-64	>64	
Total EU 27	157,000	536,000	681,000	64,000	259,000	247,000	1,945,000
W.Europe	125,000	425,000	563,000	51,000	208,000	210,000	1,581,000
E.Europe	32,000	111,000	118,000	13,000	51,000	37,000	362,000
Turkey	25,000	48,000	21,000	11,000	24,000	9,000	138,000

1.2.3 Comparison to Published Data

If we compare the prevalence calculated with our approach, there are very few countries where the recent published estimates differ, as shown below. Only the United Kingdom and Finland are somewhat different. Considering that the majority of the estimates in Alamanos' paper were crude estimates while our estimates are adjusted to the population by age and gender, and that we have a slightly higher starting age (>19), there appears no need for further adjustment.

Table 1-5 – Comparison of Estimates to Published Data

Country	Year	Estimated Prevalence %	Published Prevalence %	Population
Czech Rep	2006	0.46	0.61*	>=16
Finland	1993	0.60	0.8%*	>=16
Finland	2001	n.a.	1.8	>=65
France	1999	0.48	0.50	>=18
France	2005	0.48	031	>=18
France	2007	0.48	0.31	
Greece	1997	0.48	0.35	>=16
Greece	2003	0.48	0.70*	>=19
Greece	2006	0.48	0.67	>=19
Ireland	1999	0.49	0.50*	
Italy	1998	0.49	0.33*	>=16
Italy	2005	0.49	0.46*	>=18
Lithuania	2008	0.47	0.55	>=18
Norway	1997	0.56	0.44*	20-79
Norway	2000	0.56	0.43*	>=20
Spain	2002	0.45	0.50*	>=20
Sweden	1999	0.60	0.51*	20-74
UK	2002	0.57	0.85*	>=16
Turkey	2004	0.31	0.36*	>=20

**crude rates*

1.3 Health Burden

"Health burden" is defined here as the impact on patients' health related quality of life and their ability to perform daily activities. This topic has been addressed extensively in the previous report [28, 31], and is therefore only summarized here.

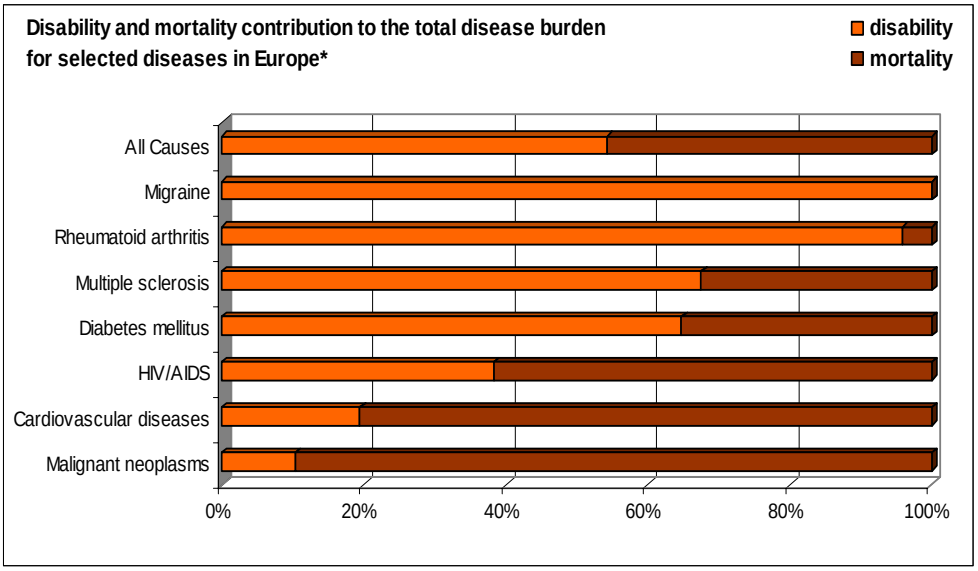
On a macro-level, where one of the key requirements is comparability across diseases, the health burden is generally measured by disability-adjusted life-years (DALY), a two-dimensional measure integrating mortality and disability (morbidity) developed by the World Health Organization [32]. In simple terms, one DALY can be thought of as one year without disability lost. The measure does thus not include health related quality of life, but is based on disability.

In health economic studies, the quality-adjusted life-year (QALY) is preferred. As the DALY, it is a two-dimensional measure, combining life-years with a weight (called utility) between 0 (representing death) and 1 (representing full health) that represents the population's preference for given health states [33]. The major differences of the QALY to the DALY are that utility does incorporate health related quality of life and that 0 and 1 are clearly anchored with reference values established with the general population.

1.3.1 DALYs in RA

The loss of DALYs is thus composed of two inputs, mortality (years of life lost) and disability (years of disability), and to compare across diseases, it is interesting to investigate which part contributes most to the measure. For the total burden of disease in Europe, the split between years of life lost and years of disability is approximately 50%-50% as shown in the figure below [32]. However the distribution between disability and mortality to the disease burden varies greatly depending on the type of disease. For RA the greatest share of the disease burden is caused by disability, whereas for cancer and cardiovascular disease premature death constitutes the largest part of the disease burden.

Figure 1-5 – The share of morbidity and mortality in the disease burden



**WHO sub-region EUR A (Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Norway, Netherlands, Portugal, San Marino, Slovenia, Spain, Sweden. Switzerland, United Kingdom)*

1.3.2 QALYs in RA

QALYs have been widely used and accepted for economic evaluation in RA. As the disease manifests itself with a number of different symptoms – swollen and tender joints, stiffness, pain, fatigues, temporary and irreversible functional disability – quality of life appears the most appropriate measure of the burden and the health gain with treatment.

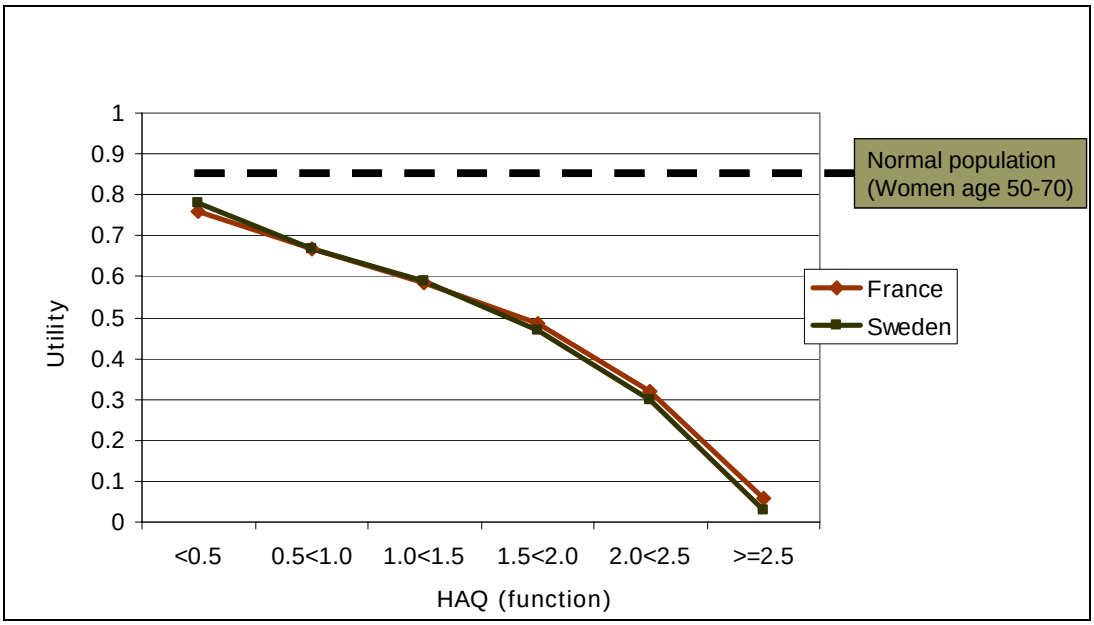
Compared to many other chronic diseases, mean utility in RA is low, as shown below. More importantly, though, a considerable number of studies have shown that it decreases rapidly right from the onset of the disease [31, 34-38]. The mean utility is thus strongly influenced by the disease severity of the sample, and small samples may produce biased results. Utility is closely correlated with functional capacity, expressed on a scale between 0 and 3 with the Health Assessment Questionnaire (HAQ). Early in the disease, HAQ is most strongly influenced by the consequences of inflammation (swollen and painful joints, fatigue) while later in the disease it is influenced by both inflammation and irreversible and painful joint erosion [39]. In addition to function, disease activity exerts an additional effect on utility, with patients with low disease activity but a similar HAQ level having higher utility than patients with high disease activity [37]. When mean utilities of patients with RA are compared to those of an age-matched sample of the general population, the loss of QALYs can be estimated at 0.2-0.3 QALYs per year, or expressed differently, a 20-30% loss of quality of life (adapted from [38])

Table 1-6 – Utilities in different chronic diseases.

Disease	*Mean utility*	*Sample size*
Other rheumatoid arthritis	**0.43**	**120**
Rheumatoid arthritis	**0.50**	**1487**
Multiple sclerosis	0.56	13186
Angina pectoris	0.57	284
Acute myocardial infarction	0.61	251
Atrial fibrillation and flutter	0.61	189
Chronic ischaemic heart disease	0.64	789
Gastro-oesophageal reflux disease	0.67	216
Crohn's disease (regional enteritis)	0.69	73
Essential (primary) hyptertension	0.69	82
Malignant neoplasm of prostate	0.72	83
Non-insulin-dependent diabetes	0.76	159
Ulcerative colitis	0.79	61

Source: adapted from Curry et al, Value in Health 2005

Figure 1-6 – Utility related to disease severity

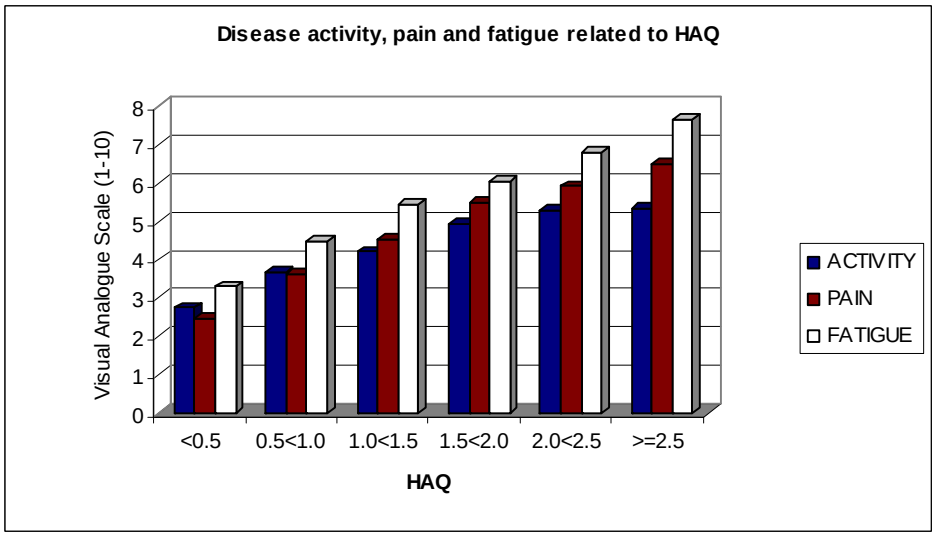


Source: Adapted from [31, 37, 38]
Utility was measured in both studies using the EQ-5D.

Measurement of utility using the EQ-5D is currently included as part of outcome measurement in some of the registries that follow patients on biologic treatments and first results are available from the Southern Swedish Registry (SSATG) [40]. (See chapter 5).

In a similar way as utility, a French study found that when patients were asked to rate the activity of their disease (inflammation), their pain and their fatigue on Visual analogue scales (1-10), all three symptoms were correlated with HAQ (adapted from [38]).

Figure 1-7 – Rating of disease symptoms



Source: adapted from [38]

1.4 Conclusions

This chapter summarizes the literature on prevalence of RA and the impact the disease has on patients. The data on the health burden, despite of the limited number of large studies, are very consistent and can essentially be applied across Europe. The data on prevalence are more difficult to interpret and we have therefore proposed an approach to estimating prevalence from existing detailed data sets. The results yields the prevalence for patients that are diagnosed rather than the estimated potential number of patients, as this is more relevant when estimating the proportion of patients that receive treatment.

1.5 References

1. Silman A, Hochberg M. Epidemiology of rheumatic diseases. Oxford: Oxford University Press; 1993.
2. Abdel-Nasser AM, Rasker JJ, Valkenburg HA. Epidemiological and clinical aspects relating to the variability of rheumatoid arthritis. Semin Arthritis Rheum 1997;27(2):123-40.
3. Kvien TK, Glennas A, Knudsrod OG, Smedstad LM, Mowinckel P, Forre O. The prevalence and severity of rheumatoid arthritis in Oslo. Results from a county register and a population survey. Scand J Rheumatol 1997;26(6):412-8.
4. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev 2005;4(3):130-6.
5. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum 2006;36(3):182-8.
6. Symmons D, Turner G, Webb R, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology (Oxford) 2002;41(7):793-800.
7. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-24.
8. Silman A, Hochberg M. Epidemiology of rheumatic diseases. Second Edition. Oxford: Oxford University Press; 2002.
9. Hakala M, Pollanen R, Nieminen P. The ARA 1987 revised criteria select patients with clinical rheumatoid arthritis from a population based cohort of subjects with chronic rheumatic diseases registered for drug reimbursement. J Rheumatol 1993;20(10):1674-8.
10. Drosos AA, Alamanos I, Voulgari PV, et al. Epidemiology of adult rheumatoid arthritis in northwest Greece 1987-1995. J Rheumatol 1997;24(11):2129-33.
11. Cimmino MA, Parisi M, Moggiana G, Mela GS, Accardo S. Prevalence of rheumatoid arthritis in Italy: the Chiavari Study. Ann Rheum Dis 1998;57(5):315-8.
12. Stojanovic R, Vlajinac H, Palic-Obradovic D, Janosevic S, Adanja B. Prevalence of rheumatoid arthritis in Belgrade, Yugoslavia. Br J Rheumatol 1998;37(7):729-32.
13. Power D, Codd M, Ivers L, Sant S, Barry M. Prevalence of rheumatoid arthritis in Dublin, Ireland: a population based survey. Ir J Med Sci 1999;168(3):197-200.
14. Saraux A, Guedes C, Allain J, et al. Prevalence of rheumatoid arthritis and spondyloarthropathy in Brittany, France. Societe de Rhumatologie de l'Ouest. J Rheumatol 1999;26(12):2622-7.

15. Simonsson M, Bergman S, Jacobsson LT, Petersson IF, Svensson B. The prevalence of rheumatoid arthritis in Sweden. Scand J Rheumatol 1999;28(6):340-3.
16. Riise T, Jacobsen BK, Gran JT. Incidence and prevalence of rheumatoid arthritis in the county of Troms, northern Norway. J Rheumatol 2000;27(6):1386-9.
17. Carmona L, Villaverde V, Hernandez-Garcia C, Ballina J, Gabriel R, Laffon A. The prevalence of rheumatoid arthritis in the general population of Spain. Rheumatology (Oxford) 2002;41(1):88-95.
18. Andrianakos A, Trontzas P, Christoyannis F, et al. Prevalence of rheumatic diseases in Greece: a cross-sectional population based epidemiological study. The ESORDIG Study. J Rheumatol 2003;30(7):1589-601.
19. Guillemin F, Saraux A, Guggenbuhl P, et al. Prevalence of rheumatoid arthritis in France: 2001. Ann Rheum Dis 2005;64(10):1427-30.
20. Akar S, Birlik M, Gurler O, et al. The prevalence of rheumatoid arthritis in an urban population of Izmir-Turkey. Clin Exp Rheumatol 2004;22(4):416-20.
21. Laiho K, Tuomilehto J, Tilvis R. Prevalence of rheumatoid arthritis and musculoskeletal diseases in the elderly population. Rheumatol Int 2001;20(3):85-7.
22. Salaffi F, De Angelis R, Grassi W. Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. Clin Exp Rheumatol 2005;23(6):819-28.
23. Hanova P, Pavelka K, Dostal C, Holcatova I, Pikhart H. Epidemiology of rheumatoid arthritis, juvenile idiopathic arthritis and gout in two regions of the Czech Republic in a descriptive population-based survey in 2002-2003. Clin Exp Rheumatol 2006;24(5):499-507.
24. Andrianakos A, Trontzas P, Christoyannis F, et al. Prevalence and management of rheumatoid arthritis in the general population of Greece--the ESORDIG study. Rheumatology (Oxford) 2006;45(12):1549-54.
25. Roux CH, Saraux A, Le Bihan E, et al. Rheumatoid arthritis and spondyloarthropathies: geographical variations in prevalence in France. J Rheumatol 2007;34(1):117-22.
26. Adomaviciute D, Pileckyte M, Baranauskaite A, Morvan J, Dadoniene J, Guillemin F. Prevalence survey of rheumatoid arthritis and spondyloarthropathy in Lithuania. Scand J Rheumatol 2008;37(2):113-9.
27. Otsa K, Tammaru M, Vorobjov S, Esko M, Pärsik E. The prevalence of rheumatoid arthritis (RA) in Harju County, Estonia. EULAR 2009 2009;Abstract FRI0517.
28. Lundkvist J, Kastang F, Kobelt G. The burden of rheumatoid arthritis and access to treatment: health burden and costs. Eur J Health Econ 2008;8 Suppl 2:S49-60.
29. National, of B, and H, Welfare. Skåne Health Care Register (SHCR). 2008;Personal communication M.Englund, MORSE project, Musculoskeletal Sciences. Lund University Hospital Sweden.
30. National, Statistics, Hungary http:\\www.ksh.hu. Patients with ICD10 code M05, M06 registered at the general practitioners' service. 2006.
31. Kobelt G, Jonsson B. The burden of rheumatoid arthritis and access to treatment: outcome and cost-utility of treatments. Eur J Health Econ 2008;8 Suppl 2:95-106.
32. WorldHealthOrganisation. Dearth and DALY estimated for 2002 by cause for WHO member states. In: WHO, Geneva; 2002.
33. Torrance G. Measurement of health state utilities for economic appraisal. A review. Journal of Health Economics 1986;5:1-30.
34. Hurst N, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: Validity, responsiveness and reliability of EuroQol (EQ-5D). British Journal of Rheumatology 1997;36:551-9.

35. Kobelt G, Eberhardt K, Jönsson L, Jönsson B. Economic consequences of the progression of rheumatoid arthritis in Sweden. Arthritis & Rheumatism 1999;42(2):347-56.
36. Kobelt G, Jönsson L, Lindgren P, Young A, Eberhardt K. Modelling the Progression of Rheumatoid Arthritis. A Two-Country Model to Estimate Costs and Consequences RA. Arthritis & Rheumatism 2002;46(9):2310-9.
37. Kobelt G, Lindgren P, Lindroth Y, Jacobson L, Eberhardt K. Modelling the effect of function and disease activity on costs and quality of life in rheumatoid arthritis. Rheumatology (Oxford) 2005;44(9):1169-75.
38. Kobelt G, Woronoff AS, Richard B, Peeters P, Sany J. Disease status, costs and quality of life of patients with rheumatoid arthritis in France: the ECO-PR Study. Joint Bone Spine 2008;75(4):408-15.
39. Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. Arthritis Rheum 2006;54(9):2784-92.
40. Gulfe A, Kristensen LE, Saxne T, Jacobsson LT, Petersson IF, Geborek P. Rapid and sustained health utility gain in anti-TNF treated inflammatory arthritis. Observational data during seven years in southern Sweden. Ann Rheum Dis 2009.

Chapter 2 - Cost of Rheumatoid Arthritis

We gratefully acknowledge the contribution of

- Marta Pentek MD PhD (Corvinius University, Budapest, Hungary) with the detailed Hungarian cost data

CONTENT

2 Cost of RA in Europe 2:2
2.1 Summary 2:2
2.2 The economic burden of RA 2:3
2.3 Modelling the Cost of RA 2:4
2.3.1 Model design 2:4
2.3.2 Model data 2:5
2.3.2.1 Costs 2:5
2.3.2.2 Economic comparative data 2:7
2.3.3 Results 2:9
2.4 Conclusion 2:13
2.5 References 2:13

TABLES

Table 2-1 – Cost differences due to perspective and calculation methods 2:3
Table 2-2 Studies included in the model calculations 2:6
Table 2-3 Relative prices and relative health care expenditures per capita 2:7
Table 2-4 Labour costs and employment rate by age 2:8
Table 2-5 estimated annual cost of RA by country, total 2:9
Table 2-6 Mean estimated annual cost per patient (€ 2008) 2:10

FIGURES

Figure 2-1 – Mean annual cost per patient with RA (€ 2008) 2:11
Figure 2-2 Structure of Costs (Western Europe) 2:12
Figure 2-3 Structure of Costs (Central/Eastern Europe) 2:12

2 Cost of RA in Europe

2.1 Summary

In this chapter, we estimate the total cost of RA in Europe, based on the cost per patient and on the prevalence of diagnosed patients.

The published literature on the cost of RA in different countries does not give a clear picture, as studies are not consistent in their approach and in the samples and data included in the analysis. In chronic progressive diseases, the influence on costs of the disease severity in the study sample is very important. Similarly, prevalence by groups of disease severity would be important to extrapolate from the cost per patient to national costs of RA. In the absence of such data, we use age as a proxy in our estimation.

We use the same age groups as in the calculation of prevalence in the previous chapter, as they take into account the differences particularly in workforce participation and income. Proportional costs for the different types of resources (health care, non-medical costs, production losses and informal care) in these groups were estimated from 3 complete datasets and applied to published data from other countries. In a cost model using economic indicators costs were then imputed to those countries without published data to estimate the cost in Europe. An exception was the cost of biologic treatments for which the actual cost per patient was extracted from international sales data.

The average cost per patient with RA in Europe was estimated at € 12,900,, with as expected a clear difference between Western Europe (€ 15,000) and Central/Eastern Europe (€ 3750). The total cost of the disease was estimated at € 25.1 billion.

These estimates are lower than what was found in our previous report. The difference is due to the facts that we use prevalence estimates for diagnosed patients only, adjusted for the age structure in the population and actual sales data for biologic drugs.

2.2 The economic burden of RA

The economic burden of a disease is a complement to information about the health burden. It captures both the direct costs for resources used for the disease within the health care system and the indirect costs for resources lost due to morbidity and premature mortality. The considerable cost, both to the health care system and to society at large of RA as a chronic progressive and potentially disabling disease has been recognized for a long time. Economic studies in the field span more than two decades and a number of reviews and summaries have been published. Estimating the incremental costs incurred due to a disease is a difficult task and it is acknowledged that cost-of-illness estimates are often surrounded with a certain degree of uncertainty. A number of facts influence the results, such as the country where the study has been performed, the study objectives, the samples included, prevalence estimates, and not the least the methodology used [1]. Major methodological issues in cost of illness studies pertain to how costs due to the disease can be separated from other unrelated costs due to co-morbidity patients may incur, what perspective is adopted for the analysis, a societal perspective (all costs regardless of who pays) or a payer perspective (only costs carried by the health and care and social systems). The largest differences will occur due to the perspective, but even within the studies using the same perspective large differences may arise due to the method of calculation, in particular the way production losses are valued, as illustrated below.

Table 2-1 – Cost differences due to perspective and calculation methods

	Perspectives *France [2]* *Annual cost per patient (N=1487; € 2005)*		***Calculation Method*** *Netherlands [3]* *Annual indirect cost per patient (N=576; € 2005)*	
	Public payers [1]	Societal	Human Capital Method	Friction Cost Method
	Mean (SD)	Mean (SD)	Mean	Mean
Direct medical costs [2]	9216 (15483)	11757 (17615)		
Direct non-medical costs [3]	136 (702)	4857 (11827)		
Indirect costs [4]	2305 (5178)	5076(11253)	278 ± 1559	4434 ± 9957
Total annual cost	**11658 (16834)**	**21690 (26238)**		

1) *Excluding complementary insurance (Mutuelles)*
2) *Health care costs*
3) *Investments, services, transport, informal care*
4) *Production losses, patients <60*

However, studies agree in their overall findings: the inflammatory activity and gradual physical impairment associated with RA leads to substantially increased health care costs and severe limitations in the ability to work. Indeed, production losses represent the largest cost in most studies. More recently, studies have also focused on the large amount of costs borne by patients and their families, due to the need to adapt the environment or for help with daily activities [4-6]. Functional disability has been identified as the major driver of all types of costs with the exception of short term sick leave which is driven by inflammation (disease activity) [7-9]. As one would expect in the case of a chronic progressive diseases, there is a strong correlation between disease activity, severity, duration, age, functional status. As individual measures, they are all correlated with costs, but overall by far the strongest driver is functional status (generally measured by HAQ) [10].

Information about the cost of a disease provides important general information to policy makers, but can not be used directly for guiding decisions about resource allocation to individual treatments. Cost-of illness studies do, however, provide important data that can serve as a basis for cost-effectiveness analyses of health interventions. In the case of RA, mean costs per patient increase with increasing functional disability (and thus with age and time). Economic evaluation will then estimate the long-term consequences of changing the course of the disease and prevent or delay the development of severe disability [1].

2.3 Modelling the Cost of RA

Costs in health economic studies are divided into direct and indirect costs:

- Direct costs are costs directly linked to the treatment, detection, prevention or care of an illness. They are further separated into medical cost, i.e. costs that occur in the health care sector, and non-medical costs that occur in other sectors, such as social services, community or patients themselves.
- Indirect costs are production losses that result as a consequence of an illness, premature death or treatment of an illness.

These definitions are used in most studies, but there is some discussion as to whether informal care should be considered a direct or an indirect cost. We choose to report them as a separate item. Informal care costs can be estimated in three different ways: production losses for those carers who work, replacement cost using as proxy the cost of professional carers, or loss of leisure time for all carers. Data on informal care are rather scarce in the data at our disposal, and we therefore present informal care as a separate item in this report. Other non-medical costs such transportation, social services, etc are integrated into direct costs.

2.3.1 Model design

We developed a model, based on earlier work [11] that allows estimating the cost of RA in Europe despite a considerable lack of data in many countries. The model uses data on the cost per patient from published studies and comparative economic indexes to estimate costs for countries where cost data are missing or incomplete in the following way:

- Health care costs (direct medical costs) are imputed using the healthcare spending per capita and the comparative price levels in health care;

- Non-medical costs were calculated differently depending on the type
    - Cost of goods (devices and investments) were imputed using national price levels;
    - Cost for services were adjusted by the cost of labour in health care;
    - Informal care, estimated as the cost of leisure time estimated from disposable income after tax, was imputed using the comparative index of cost of labour;
    - Production losses imputed using the comparative index of cost of labour and level of work participation in each country by age group and sex.

The costs per patient estimated are then combined with the country-specific prevalence to obtain the total cost of RA per country included the report.

The model can thus be likened to a prevalence-based cost of illness study that estimates total annual costs for a prevalent patient population, based on the mean annual cost per patient. These latter costs can be estimated using either aggregated resource consumption from available statistics, or by collecting actual resource consumption in a representative sample of patients. We based our cost estimates on an analysis of patient data from France, Hungary and Sweden and on published cost studies, most of which had collected data from patients.

For the model, costs were divided into medical costs, drugs, non-medical costs, informal care and production losses (indirect costs). Non-medical costs were further separated into services (formal help in home, transportation) and products (aids/devices/adaptations/other). In a first step, available annual costs per patients for each of these categories were extracted from the studies identified in the literature review. In a second step these costs were inflated to the same base year (2008) using country specific consumer price indexes (CPI). Finally, costs were adjusted into a common currency (Euro), using 2008 average exchange rates.

The prevalence of RA was estimated in three age groups, 20-44 years, 45-64 years, and >64 years (see chapter 1) and costs were calculated for the same age groups. This allows a much more precise calculation of in particular production losses, as salary levels tend to be different between the two first age groups and not calculated for retired patients. Although retirement age varies slightly between the countries, we used 65 as the generally accepted age.

In countries for which cost studies were available, these data were used in the model, with costs updated to 2008 value and converted to Euros. Imputations were thus only made for countries where no or not enough data could be identified.

2.3.2 Model data

2.3.2.1 Costs

A comprehensive literature review was conducted to identify studies relevant for the purpose of this cost study. PubMed, Health Economic Evaluations Database (HEED), and reports from various research institutes were included in the searches. Studies that evaluated the cost of a representative sample of RA patients were included. This means that cost data from studies assessing cost of patients undergoing a particular treatment, studies assessing costs of newly diagnosed patients only, etc. were not included in the analysis.

Costs were separated into the categories mentioned above: medical costs, drugs, non-medical costs, informal care and indirect costs. The studies identified were reviewed in detail and one study per country (and cost category, as applicable) was selected as basis for the international comparison. The selection was based on the completeness of the study, quality of study methodology, patient population included and year of data collection.

For three of these studies (France, Sweden, Hungary [2, 12, 13]), the raw data were available and cost estimates were refined by age and gender. For a fourth study (Denmark –[14]) it was possible to estimate cost by age from the publication. The proportional distribution of costs by age group and gender thus estimated were then applied to the age range and mean age of the patients in the published data from other countries. Average cost per patient were hence calculated by the age groups defined earlier, 20-44, 45-64 and >65, and by gender.

The studies included in the final cost analysis are shown below, with all costs updated with the CPI of the specific country and converted to € 2008.

Table 2-2 Studies included in the model calculations

Country	*Author*	*Year of cost data*	*Age mean/ (range)*	*Years with RA (mean)*	*n*	*Annual cost of RA (€ 2008)*
						Annual total cost of RA (€ 2008)
France	Recalculated from Kobelt [2]	2005	/(20-44)	12	133	€ 23,461
France	idem	2005	/(45-64)	16	631	€ 30,188
France	idem	2005	/(65+)	21	722	€ 15,097
Sweden	Unpubished data, updated from Jacobsson and Kobelt [12]	2008	/(20-44)	9	126	€ 14,331
Sweden	Idem	2008	/(45-64)	13	442	€ 23,554
Sweden	idem	2008	/(65+)	18	478	€ 5,607
Portugal	Pedro [15]	2008	57/	16	713	€ 5,808
Hungary	Recalculated from Pentek [13]	2004	/(20-44)	6	39	€ 6,160
Hungary	Idem	2004	/(45-62)	9	155	€ 6,576
Hungary	idem	2004	/(62+)		60	€ 2,866
						Annual direct cost of RA (€ 2008)
Belgium	Westhovens [16]	2005	57/(24-76)	6.5	133	€ 8,240
Austria	Wagner [17]	2005	61/(27-83)	16	210	€ 7,269
Denmark	Sørensen [14]	2004	/(20-44)			€ 1,912
Denmark			/(45-64)			€ 3,371
Denmark			/(65+)			€ 2,933
						Annual indirect cost of RA (€2008)
Finland	Puolakka	2006	/45-49	5-8	162	€ 7,893

2.3.2.2 Economic comparative data

Data on health care expenditure, price levels, labour costs as well as population statistics were obtained from WHO [18] and Eurostat [19] and are presented in table below. Information not available in Eurostat, e.g. some data for the non-EU countries, was taken from national statistics databases for the specific countries [20, 21].

Table 2-3 Relative prices and relative health care expenditures per capita in the countries included [18, 19]

	Comparative price level index EU27 - Health 2007	*Health expenditure per capita 2005 (PPP €)*	*Comparative health exp per capita index EU27*
EU27	100	1,755	100
Austria	107	2,417	137
Belgium	110	2,132	120
Bulgaria	29	642	36
Cyprus	102	902	51
Czech Republic	47	1,255	71
Denmark	152	1,940	110
Estonia	53	663	37
Finland	127	1,511	85
France	107	2,426	137
Germany	103	2,403	136
Greece	81	2,178	123
Hungary	54	1,074	61
Iceland	170	2,061	116
Ireland	131	2,072	117
Italy	123	1,491	84
Latvia	44	686	39
Lithuania	46	665	38
Luxembourg	123	3,504	198
Malta	58	1,450	82
Netherlands	101	2,400	136
Norway	159	2,530	143
Poland	44	758	43
Portugal	87	1,403	79
Romania	37	464	26
Slovakia	51	828	47
Slovenia	71	1,427	81
Spain	84	1,737	98
Sweden	123	2,056	116
Switzerland	138	2,798	158
United Kingdom	117	1780	101
Turkey	58	452	26

Table 2-4 Labour costs and employment rate by age [19]

	Monthly labour cost EU27 - All branches		*Monthly labour cost EU27 - Health and social work*		*% employed (20-44 yrs)*		*% employed (45-64 yrs)*	
	€ 2006	**Comparative levels (EU27=100)**	**€ 2006**	**Comparative levels (EU27=100)**	**women**	**men**	**women**	**men**
EU27	3,117	100	2,723	100	68%	83%	54%	71%
Austria	3,827	123	3,373	124	76%	89%	55%	72%
Belgium	4,047	130	2,960	109	70%	81%	48%	67%
Bulgaria	243	8	255	9	70%	78%	56%	67%
Cyprus	2,091	67	2,546	67[E]	76%	88%	56%	84%
Czech Republic	1,028	33	982	36	66%	86%	58%	75%
Denmark	4,481	144	3,423	126	81%	89%	67%	77%
Estonia	840	27	782	29	71%	85%	74%	75%
Finland	3,685	118	2,725	100	75%	84%	70%	69%
France	4,382	141	:	141[E]	71%	82%	58%	66%
Germany	3,868	124	3,333	122	73%	83%	61%	74%
Greece	:	71[A]	:	71[E]	59%	83%	42%	76%
Hungary	947	30	841	31	60%	77%	50%	60%
Iceland	5,032	161	:	161[E]	81%	91%	82%	93%
Ireland	:	128[D]	:	128[E]	70%	86%	54%	78%
Italy	:	104[B]	:	104[E]	57%	81%	41%	69%
Latvia	532	17	534	20	73%	83%	68%	75%
Lithuania	646	21	586	22	72%	78%	66%	74%
Luxembourg	4,625	148	4,850	178	69%	85%	49%	68%
Malta	1,445	46	1,592	58	53%	88%	19%	68%
Netherlands	:	133[C]	:	133[E]	80%	91%	59%	77%
Norway	:	152[D]	:	152	81%	86%	73%	81%
Poland	889	29	697	26	64%	77%	44%	60%
Portugal	1,618	52	1,872	69	72%	83%	58%	74%
Romania	414	13	457	17	63%	74%	50%	67%
Slovakia	775	25	621	23	64%	79%	51%	70%
Slovenia	1,673	54	1,922	71	78%	85%	53%	67%
Spain	2,203	71	2,439	90	66%	84%	45%	75%
Sweden	4,518	145	3,765	138	78%	85%	75%	80%
Switzerland	:	138[D]	:	138[E]	77%	91%	70%	85%
Turkey	624 [21]	20	:	20[E]	27%	81%	20%	59%
United Kingdom		137	4,258	156	72%	86%	63%	77%

[A]Based on data from 2003, [B]Based on data from 2002, [C]Based on data from 2005, [D]Extrapolation from 2006 OECD data, [E]Based on data for all branches

2.3.3 Results

We estimate that there are currently 1.9 million patients with a diagnosis of RA in Europe (EU 27 and EU 30 including Iceland, Norway, Switzerland) as well as Turkey. The total cost of RA in EU 27 was estimated to € 24 billion.

Table 2-5 estimated annual cost of RA by country, total

Country	*Total cost of RA (€ 2008)*	*Total prevalent cases of RA*
Austria	420,666,022	30,536
Belgium	618,317,047	39,209
Bulgaria	61,295,241	29,711
Cyprus	19,822,623	2,422
Czech Republic	223,950,063	37,037
Denmark	399,385,899	23,676
Estonia	20,133,404	5,124
Finland	339,073,147	24,279
France	4,653,453,492	226,750
Germany	6,179,460,256	328,844
Greece	487,911,658	42,574
Hungary	198,934,391	37,907
Iceland	22,929,557	1,085
Ireland	253,251,076	15,035
Italy	2,723,687,485	235,898
Latvia	27,707,292	8,771
Lithuania	41,166,056	12,213
Luxembourg	33,288,628	1,589
Malta	9,707,362	1,419
Netherlands	1,027,487,886	56,934
Norway	402,987,901	19,468
Poland	489,374,432	131,546
Portugal	295,031,406	39,379
Romania	162,387,179	74,832
Slovakia	74,879,157	17,567
Slovenia	58,854,828	7,461
Spain	1,586,356,683	159,535
Sweden	543,107,075	41,576
Switzerland	536,933,367	27,469
United Kingdom	3,163,265,560	263,672
Turkey	320,917,123	137,905
Total EU27	**24,072,620,328**	**1,895,497**
Total Europe	**25,074,806,172**	**1,943,519**
Total Western Europe	**23,716,124,129**	**1,581,350**
Total Eastern Europe	**1,358,682,043**	**362,169**

The estimated mean annual cost per patient in the study countries ranged from €2,000 to €21,000.

Table 2-6 Mean estimated annual cost per patient (€ 2008)

Country	*Total cost per patient*	*Direct cost (excl.biol)*	*Biologics*	*Informal Care*	*Indirect Cost*
	Mean, €	*Mean, €*	*Mean, €*	*Mean, €*	*Mean, €*
Austria	13,776	5,515	444	2,528	5,289
Belgium	15,770	3,959	2,222	4,606	4,983
Bulgaria	2,063	1,552	13	160	338
Cyprus	8,185	2,532	818	1,355	3,480
Czech Republic	6,047	3,144	616	670	1,618
Denmark	16,869	4,648	2,213	2,969	7,039
Estonia	3,929	1,742	254	556	1,377
Finland	13,965	4,243	1,645	2,448	5,631
France	20,522	10,252	1,475	1,284	7,512
Germany	18,791	7,261	1,284	2,576	7,670
Greece	11,460	5,551	1,952	1,466	2,492
Hungary	5,248	1,763	411	837	2,237
Iceland	21,135	5,885	2,005	3,299	9,946
Ireland	16,844	5,645	2,716	2,616	5,867
Italy	11,546	4,552	731	3,290	2,972
Latvia	3,159	1,728	254	352	825
Lithuania	3,371	1,688	254	426	1,003
Luxembourg	20,949	9,314	2,361	3,026	6,248
Malta	6,842	3,753	818	939	1,332
Netherlands	18,047	7,847	1,543	2,214	6,442
Norway	20,700	6,960	2,740	3,149	7,851
Poland	3,720	1,922	88	579	1,132
Portugal	7,492	4,453	818	1,070	1,151
Romania	2,170	1,187	170	272	542
Slovakia	4,263	2,052	549	502	1,160
Slovenia	7,888	3,797	648	1,099	2,344
Spain	9,944	5,383	1,443	1,456	1,662
Sweden	13,063	3,543	2,158	496	6,866
Switzerland	19,547	7,450	1,793	2,835	7,470
United Kingdom	11,997	5,265	888	2,837	3,008
Turkey	2,327	1,126	170	387	645
Average Europe	**12,902**	**5,512**	**1,028**	**2,012**	**4,289**
Western Europe	14,997	6,345	1,285	2,355	5,012
Eastern Europe	3,752	1,878	232	513	1,128

Figure 2-1 – Mean annual cost per patient with RA (€ 2008)

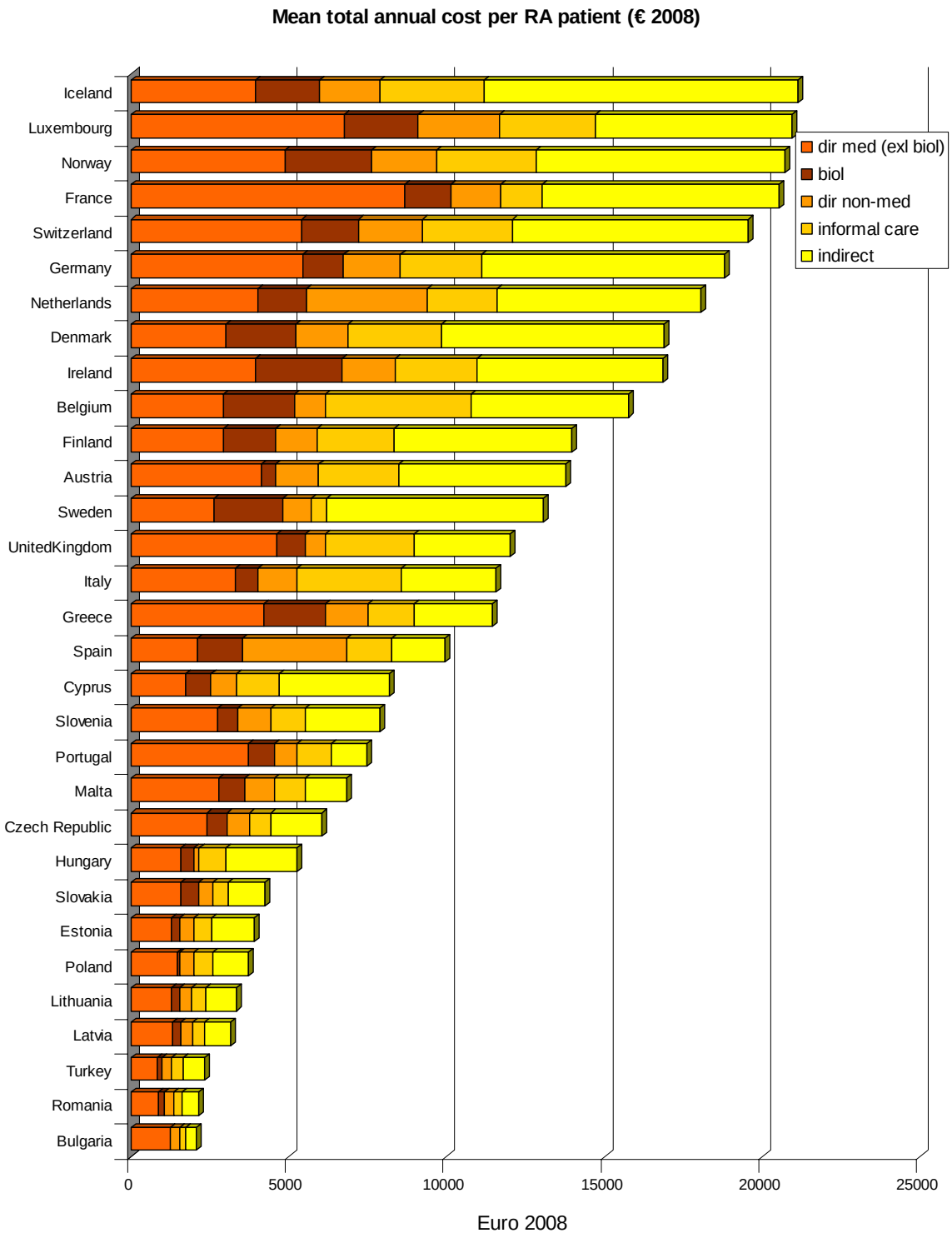


Figure 2-2 Structure of Costs (Western Europe)

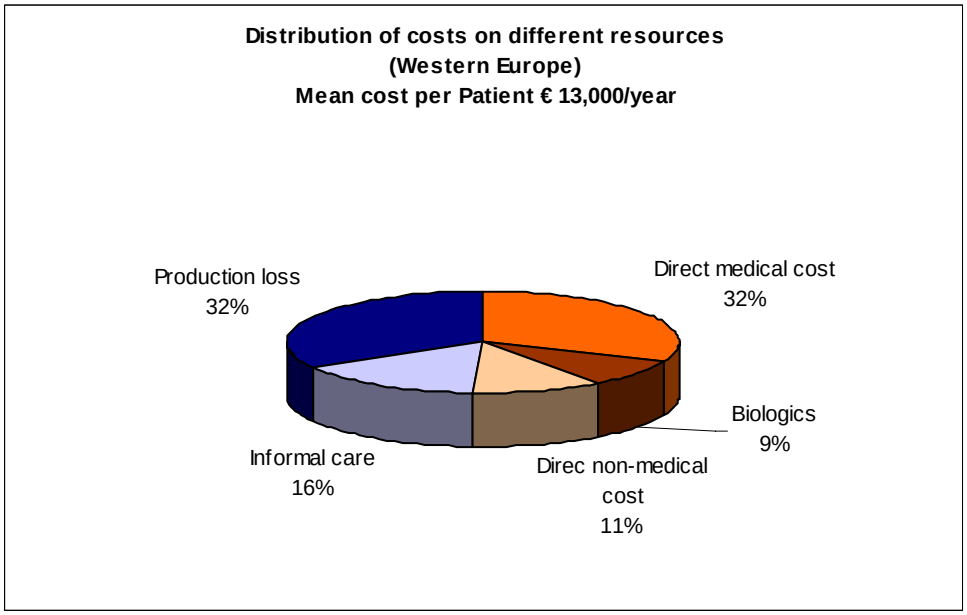
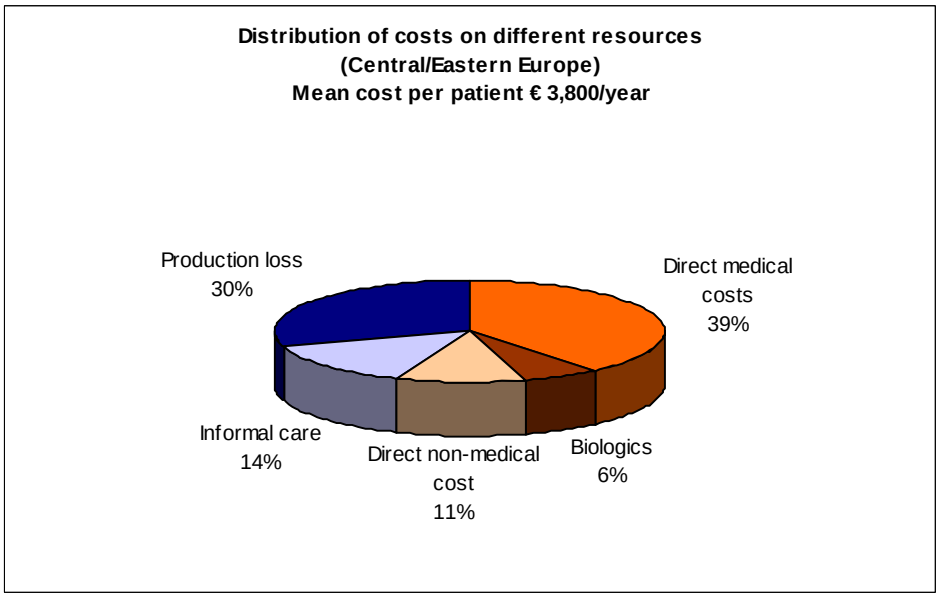


Figure 2-3 Structure of Costs (Central/Eastern Europe)



As in previous studies, we found that costs outside the health care sector dominate costs: production losses, informal care, non-medical costs are often only partially reimbursed. Total costs per patient between the old and new EU countries, with biologics representing a larger proportion of substantially higher costs in Western Europe. In the societal perspective, biologic treatments are estimated to represent 20% of health care costs in Western Europe, 12% in Central and Eastern Europe.

However, costs outside the health care sector continue to dominate costs in RA in all countries.

2.4 Conclusion

In this chapter, we have refined the previous estimates of the cost of RA by using a different calculation of the number of prevalent and diagnosed patients, as well as new information on the costs per patient and type of resource by age and gender. This has yielded a considerably lower estimate than in our earlier report, explained by

- a lower overall prevalence, around 0.5 versus around 0.6
- using actual sales per patient of biologic drugs, rather than impute usage from published studies, which yielded in an overestimation of biologics costs in particular in Eastern and Central European countries
- to a lesser extent, selecting only one country per study with the most complete data rather than all available studies.

2.5 References

1. Kobelt G. Health economic issues in rheumatoid arthritis. Scand J Rheumatol 2006;35(6):415-25.
2. Kobelt G, Woronoff AS, Richard B, Peeters P, Sany J. Disease status, costs and quality of life of patients with rheumatoid arthritis in France: the ECO-PR Study. Joint Bone Spine 2008;75(4):408-15.
3. Verstappen SM, Boonen A, Verkleij H, Bijlsma JW, Buskens E, Jacobs JW. Productivity costs among patients with rheumatoid arthritis: the influence of methods and sources to value loss of productivity. Ann Rheum Dis 2005;64(12):1754-60.
4. Kobelt G, Lindgren P, Lindroth Y, Jacobson L, Eberhardt K. Modelling the effect of function and disease activity on costs and quality of life in rheumatoid arthritis. Rheumatology (Oxford) 2005;44(9):1169-75.
5. Huscher D, Merkesdal S, Thiele K, Zeidler H, Schneider M, Zink A. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. Ann Rheum Dis 2006;65(9):1175-83.
6. Hulsemann JL, Mittendorf T, Merkesdal S, et al. Direct costs related to rheumatoid arthritis: the patient perspective. Ann Rheum Dis 2005;64(10):1456-61.
7. Kobelt G, Eberhardt K, Jonsson L, Jonsson B. Economic consequences of the progression of rheumatoid arthritis in Sweden. Arthritis Rheum 1999;42(2):347-56.
8. Kobelt G, Jonsson L, Lindgren P, Young A, Eberhardt K. Modeling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. Arthritis Rheum 2002;46(9):2310-9.
9. Lajas C, Abasolo L, Bellajdel B, et al. Costs and predictors of costs in rheumatoid arthritis: a prevalence-based study. Arthritis Rheum 2003;49(1):64-70.
10. Kobelt G, Lindgren P, Singh A, Klareskog L. Cost effectiveness of etanercept (Enbrel) in combination with methotrexate in the treatment of active rheumatoid arthritis based on the TEMPO trial. Ann Rheum Dis 2005;64(8):1174-9.
11. Andlin-Sobocki P, Jonsson B, Wittchen HU, Olesen J. Cost of disorders of the brain in Europe. Eur J Neurol 2005;12 Suppl 1:1-27.
12. Jacobsson LT, Lindroth Y, Marsal L, Juran E, Bergstrom U, Kobelt G. Rheumatoid arthritis: what does it cost and what factors are driving those costs? Results of a

survey in a community-derived population in Malmo, Sweden. Scand J Rheumatol 2007;36(3):179-83.
13. Pentek M, Kobelt G, Czirjak L, et al. Costs of rheumatoid arthritis in Hungary. J Rheumatol 2007;34(6):1437.
14. Sorensen J. Health care costs attributable to the treatment of rheumatoid arthritis. Scand J Rheumatol 2004;33(6):399-404.
15. Pedro S, Ethgen O, Michaud K. Direct and indirect costs and their predictors in patients with rheumatoid arthritis in Portugal. Ann Rheum Dis 2008;67(Suppl.1):574.
16. Westhovens R, Boonen A, Verbruggen L, et al. Healthcare consumption and direct costs of rheumatoid arthritis in Belgium. Clin Rheumatol 2005;24(6):615-9.
17. Wagner E, Lackerbauer E, Siegmeth W. [Direct and indirect costs of rheumatoid arthritis and the socio-emotional effects of this disease--an Austrian study]. Wien Med Wochenschr 2005;155(9-10):217-26.
18. WHOSIS (World Health Organization Statistical Information System). Core Health Indicators 2008 Database. Geneva. [Online at:http://www.who.int/whosis/database/].
19. Eurostat Database [Online at: http://epp.eurostat.ec.europa.eu].
20. Statistics Iceland, [Online at: http://www.statice.is/].
21. Turkish Statistical Institute [Online at: http://www.turkstat.gov.tr].

Chapter 3 - Uptake of Biologic Treatments

We gratefully acknowledge the contribution of Per Troen, IMS Health, London, for help with interpretation of IMS data.

CONTENT

3 Uptake of Biologic Treatments 3:2
3.1 Summary 3:2
3.2 Methods 3:3
3.2.1 Data 3:3
3.2.2 Treatments 3:5
3.2.2.1 Use in RA 3:5
3.2.2.2 Prices 3:6
3.3 Results 3:7
3.3.1 Sales and Market Share 3:7
3.3.2 Uptake of Treatments 3:9
3.3.2.1 The 5 Large Markets (illustration of calculations) 3:9
3.3.2.2 Nordic Area, Ireland 3:12
3.3.2.3 Small Western European Countries 3:13
3.3.2.4 New EU member states 3:14
3.3.2.5 Comparison of E13 countries 3:15
3.3.2.6 Analysis by Drug – 5 Large Markets 3:16
3.3.2.7 Proportion of patients treated across Europe 3:18
3.4 Conclusion 3:19

TABLES

Table 3-1 – Adjustments made to IMS dataset 3:4
Table 3-2 Year of introduction and European sales 3:5
Table 3-3 Sales per 100,000 population in the 4th quarter 2008 (IMS) 3:7

FIGURES

Figure 3-1 Estimated European Market Shares (sales per prevalent patient) 3:7
Figure 3-2 Estimated sales per country (per 100,000 population) 3:8
Figure 3-3 Estimated total number of patients treated (5 large markets) 3:9
Figure 3-4 Estimated drug quantity per prevalent patient (5 large markets) 3:10
Figure 3-5 Estimated annual sales (€ 2008) per prevalent patient (5 large markets) 3:10
Figure 3-6 Estimated proportion of patients on treatment 3:11
Figure 3-7 Estimated total number of patients treated (Nordic Area) 3:12
Figure 3-8 Estimated proportion of patients on treatment (Nordic Area) 3:12
Figure 3-9 Estimated total number of patients treated (small W.European markets) 3:13
Figure 3-10 Estimated proportion of patients on treatment (small W.EU markets) 3:13
Figure 3-11 Estimated total number of patients treated (new EU countries) 3:14
Figure 3-12 Estimated proportion of patients on treatment (new EU countries) 3:14
Figure 3-13 Proportion of patients on treatment in E13 countries 3:15
Figure 3-14 – Sales per patient (€ 2008), E13 ..... 3:15
Figure 3-15 Proportion of patients treated with different drugs (etanercept) 3:16
Figure 3-16 Proportion of patients treated with different drugs (infliximab) 3:16
Figure 3-17 Proportion of patients treated with different drugs (adalimumab) 3:17
Figure 3-18 Proportion of patients treated with different drugs (abatacept) 3:17
Figure 3-19 Proportion on treatment end of 2008 ..... 3:18

3 Uptake of Biologic Treatments

3.1 Summary

This chapter provides a description of current access to biologic treatments. In the absence of readily available information on the number of patients treated in any country in Europe, we use international sales data on volume (mg) and price (in €) form IMS, as well as estimated prevalence in each country to derive the number of patients treated.

IMS data are incomplete in some countries, and this has been systematically verified both with manufacturers of biologic drugs and IMS staff. However, in most cases it has not been possible to identify comparable data that could be incorporated into the IMS data set, and limited adjustments were therefore made.
Four of the 6 treatments included in the analysis are used in more than one indication, but no information on the proportion of drug used in the indication RA could be obtained. We have therefore used our own best estimates.

Results are presented as drug quantity and sales (€) per prevalent patient (using prevalence estimates presented in chapter 1), and the estimated proportion of treated patients. We also present the total number of patients estimated to be on treatment in each country.

3.2 Methods

In order to discuss what factors determine access to new therapies, a description of the current access is required. Ideally, this would be information on the number of patients actually treated in each country and for what indication, as well as what proportion of patients this represents. Unfortunately, such data are not readily available, and one might think that such primary information would improve the discussion regarding access. Currently, the necessary information has to be derived indirectly.

We will use overall sales data from IMS (volume and value) and average annual dose per patient and drug to estimate the number of patients treated in each country. These data are then combined with our prevalence estimates (chapter 1) to estimate the proportion of patients treated and the mean cost per prevalent patient. This cost, in turn, is used as an input into the cost model to estimate the total cost of the disease in Europe.

3.2.1 Data

IMS data are currently the only source of comparative data at an international level, despite a number of shortcomings. It is likely that in no country are 100% of sales captured, but it is difficult to define the magnitude of underestimation. Similarly, it is possible that sales are overestimated in some countries as a consequence of the sample of pharmacies and hospitals that provide data. We have thus refrained from an overall adjustment to the data. Individual country issues and adjustments have been discussed with IMS.

For some countries it is known that part or all of hospital sales are omitted and certain wholesalers or other channels of distribution not included. In some cases, IMS data do partially adjust for this within the data set. This is for instance the case in the United Kingdom where some data at regional level (Scotland) are lacking, but this is adjusted for in the national data set. In Portugal, only hospital sales are available, but as biologics are essentially used within the hospital setting, we felt that this was not a large issue. In Austria, not all hospital sales are captured and no adjustment made for this. Consequently, we adjusted sales slightly upwards (5%). Hospital sales are not or not fully captured in Greece, Luxembourg, Ireland and the Baltic States. For the first three countries, sales appear comparatively high and one might suspect that not all parallel export sales have been excluded. Prices in these 3 countries are similar as in most other countries but considerably lower than in Germany where parallel import is known to take place. For this reason, and in the absence of any other data sets, we have not made any adjustments. For the Baltic States, we obtained a secondary data set from Estonia that allowed estimating the number of patients on treatment. The Estonian proportion of patients on treatment was then also used for Latvia and Lithuania. Finally, no data at all were available for Cyprus, Iceland and Malta. For these countries, we imputed sales from countries with similar GDPs and similar health care spending per capita. Turkey was not included in this analysis.

Table 3-1 – Adjustments made to IMS dataset

Country	Reason or data source	Adjustment
Austria	Incomplete hospital sales	+5%
Cyprus	No data	Imputation of Portuguese data
Estonia	Local sales data base (kg)	Actual quantities from Estonia from 2004 – 1st qt 2008
Greece	No hospital sales	none
Iceland	No data	Imputation of average sales in Denmark, Sweden, Finland
Ireland	No hospital sales	none
Luxembourg	No hospital sales	none
Latvia	Limited data	Imputation of Estonian data
Lithuania	Limited data	Imputation of Estonian data
Malta	No data	Imputation of Portuguese data
Portugal	Hospital data only, from 2004	none

Another difficulty may arise from parallel trade. Although drugs launched in the last 2 decades have generally a rather narrow price band across Europe, traditional price control mechanisms, adaptation to distribution channels and currency fluctuations have led to some price differences. As the price of biologic treatments is comparably high, even small differences make parallel trade worthwhile. The higher than average price in Germany has indeed led to parallel import from a number of countries, but the magnitude is difficult to estimate. Within the IMS data, this should be adjusted for, but it is difficult to verify whether there is no double-counting at all. We have approached the issue by verifying the data from Norway where parallel export to Germany is known to exist. Data from Farmastat in Norway indicate similar sales as IMS. Farmastat collects sales from wholesalers, and wholesalers are legally obliged to exclude parallel export. Several sources within the health insurance in Norway estimate the number of patients treated to be around 6000, which coincides with our calculations from IMS data. We therefore made no adjustment for Norway. The high proportion of patients treated in our Norwegian estimates may be due to two factors: 1) prevalence is underestimated, as a very high prevalence had been reported for Northern Norway, and 60% sales occur in that region, despite low population density; 2) the fastest growing segment are skin diseases, and our estimate of the proportions of drugs sold in RA may be too high for that reason.

Overall, all our verifications indicated that IMS data are a solid source in most countries for international comparison purposes.

3.2.2 Treatments

3.2.2.1 *Use in RA*

The first biologic treatments for RA, etanercept and infliximab, were introduced for the indication of RA in 1998, followed by anakinra in 2001, adalimumab in 2003 and most recently rituximab and abatacept in 2006. The three TNF-α inhibitors Etanercept, infliximab and adalimumab have subsequently been approved for further indications: ankylosing spondylitis, psoriatic arthritis, psoriasis, juvenile arthritis, Crohn's disease, ulcerative colitis, as shown above.

The additional indications have been approved in a different sequence for different drugs, but also in the different countries. Data on the proportion of drug used in RA are unfortunately available neither from IMS nor from the individual manufacturers. Similarly, rituximab has long been on the market for Non-Hotchkins' Lymphoma, and information on the proportion sold for RA is not available from IMS or the manufacturer.

As a consequence, it was necessary to make an assumption on the use in RA for these 4 products. Under the circumstances, and although for some countries the share could possibly have been established by other means, only an overall estimate for Europe rather than estimates for each individual country was made. We used the years of introduction of each additional indication for each individual drug to estimate yearly shares.

Two of the products are exclusively used in rheumatoid arthritis (anakinra, abatacept). Rituximab sales in RA are likely to between 5-10% in 2008, but can be estimated to be considerably higher in the United Kingdom where the preliminary NICE guidance has recommended its use after failure of the first TNF-inhibitor. In the absence of more precise information, we used an arbitrary number of 10% in all countries. For the TNF-inhibitors, we estimated that 65% of etanercept and adalimumab, and 45% of infliximab were used in RA. It is likely that these proportions are at the higher end for countries where the additional indications have been introduced very rapidly, e.g. in Northern Europe, but lower in countries where new indications are approved slowly, e.g. Central and Eastern Europe. However, in the absence of actual data, we have not differentiated between countries.

The table below shows the year of first introduction in Europe (EMEA approval), as well as our estimates of the proportion of sales currently in RA.

Table 3-2 Year of introduction and European sales

	RA	AS	PS	PsA	CD	UC	Sales for RA
Etanercept	2000	2004	2004	2002	-	-	**65%**
Infliximab	1999	2003	2005	2006	2006	2006	**45%**
Adalimumab	2003	2006	2007	2005	2007	-	**65%**
Anakinra	2001	-	-	-	-	-	**100%**
Rituximab	2006	-	-	-	-	-	**10%**
Abatacept	2006	-	-	-	-	-	**100%**

RA=rheumatoid arthritis; AS = ankylosing spondylitis; PS = psoriasis; PsA = psoriatic arthritis; CD = Crohn's disease; UC = ulcerative colitis

3.2.2.2 ***Prices***

Overall, the drugs are priced at a comparable ex-factory level:

- Etanercept and adalimumab have an average ex-manufacturer price of around € 13,000/treatment year in most countries.
- Abatacept is priced closer to € 14,000/treatment year, as it is indicated I most countries for patients that have failed a first biologic treatment.
- Infliximab is priced lower, around € 9,000/treatment year, when used at the label dose. However as the dose is ankylosing spondylitis is higher and thus a large amount of safety data for a higher dose are available, there appears to be a tendency to increase the dose in RA as well for patients with insufficient response. An analysis of the Southern Swedish registry found that the average dose over 3 years was 26 ampoules/year rather than around 22 ampoules/year. This increases the cost most likely to a similar level as the other biologics.
- Rituximab has a similar price as infliximab, if infusions are given on average in 6-month or longer intervals, as shown in the clinical trials. Shorter intervals will increase to cost to similar levels as the other biologics.

The end-user price in the different countries will show a greater variation, as wholesale and retail margins are different. However, biologics in many countries don't follow the standard distribution channels: A large part is sold via hospitals and standard whole-sale and pharmacy mark-ups do not apply. Also, in some countries special arrangements for distribution margins exist. Details are not available for all countries and our calculations are thus based on the ex-factory price.

Today, clinicians have thus a considerable number of treatments at their disposal that have a similar price in most countries and a similar effectiveness, but differ somewhat in their adverse effect profile and importantly by their route of administration (self-injection and infusion). The choice of which drug to use first, and in what sequence further drugs should be used, is thus rarely influenced by the price but remains with the clinician and patient. Clinicians are likely to give a high level of importance to the side-effect profile, while patients will have a strong input regarding route of administration.

3.3 Results

Results are presented as estimated sales per product in the 4th quarter 2008 per 100,000 population by country and estimated market shares in the 4th quarter 2008 using sales per prevalent patient. For completeness, we also present estimated total sales per 100,000 population by individual country. Finally, up-take curves over time in the different markets are presented.

3.3.1 Sales and Market Share

As mentioned earlier, market shares in RA are based on our own estimates of the proportion of drugs that is being used for the indication of RA.

Table 3-3 Sales per 100,000 population in the 4th quarter 2008 (IMS)

	Estimated Sales in RA	*Sales Europe 4th Qt 2008*
		€/100'000 population
Etanercept	65%	75,600
Infliximab	45%	46,500
Adalimumab	65%	77,000
Anakinra	100%	1,400
Rituximab	10%	3,900
Abatacept	100%	1,700

Figure 3-1 Estimated European Market Shares (sales per prevalent patient)

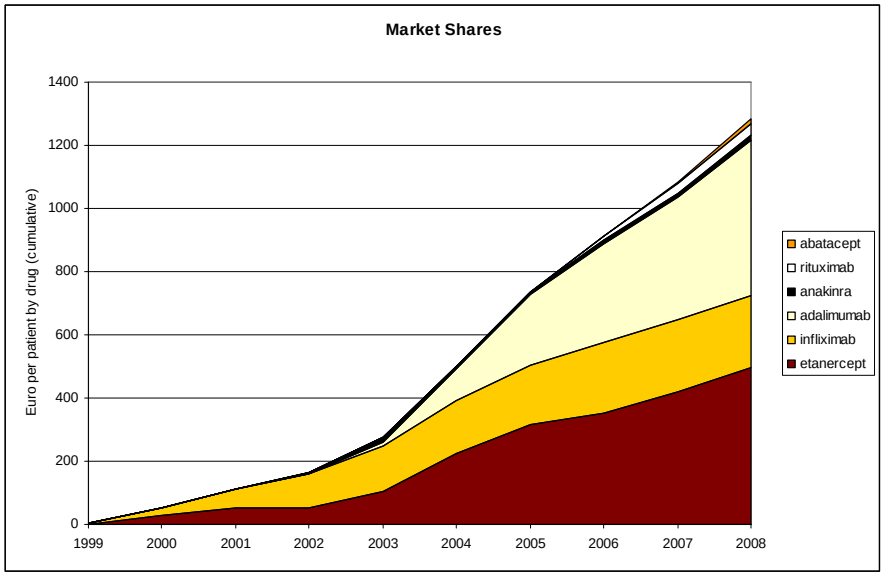
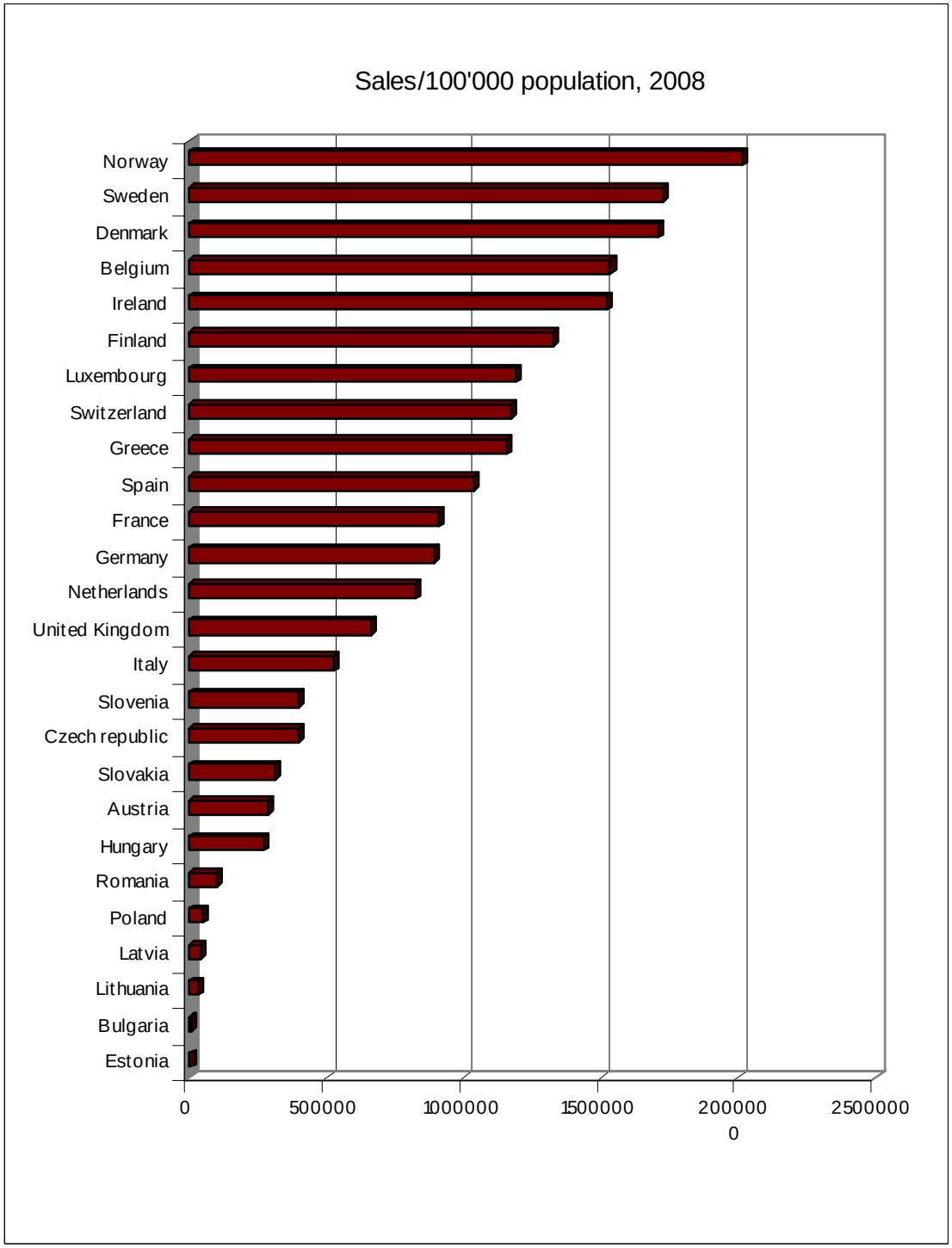


Figure 3-2 Estimated sales per country (per 100,000 population)



Sales are based on our estimates of the proportions of each drug used in RA and represent sales recorded by IMS, without corrections or imputations.

3.3.2 Uptake of Treatments

Uptake curves are based on three main inputs: drug quantities (mg) used, sales per 100,000 population and prevalent patients.

For the quantities, we estimated average annual dosages for each drug to calculate the absolute number of patients treated. This was then related to the estimated number of prevalent patients in each country (see chapter 1) to calculate the proportion of patients on treatment, the average cost as well as the average drug quantity per prevalent patient.

For this calculation, we have assumed full treatment years. The actual number of patients who have access to biologics is therefore probably somewhat higher, as patients may be off treatment for some months (e.g. between treatment switches), or even be treated intermittently.

We illustrate below these calculations for the five big markets. Subsequently, we will concentrate on the absolute number of patients and the proportion of prevalent patients on treatment. E13 represents the average for western European countries where data appear complete (Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom).

The average cost per patient estimated here has been adjusted for estimated total cost of biologics (including estimated margins and infusion costs) into our cost model in chapter 2.

3.3.2.1 *The 5 Large Markets (illustration of calculations)*

Figure 3-3 Estimated total number of patients treated (5 large markets)

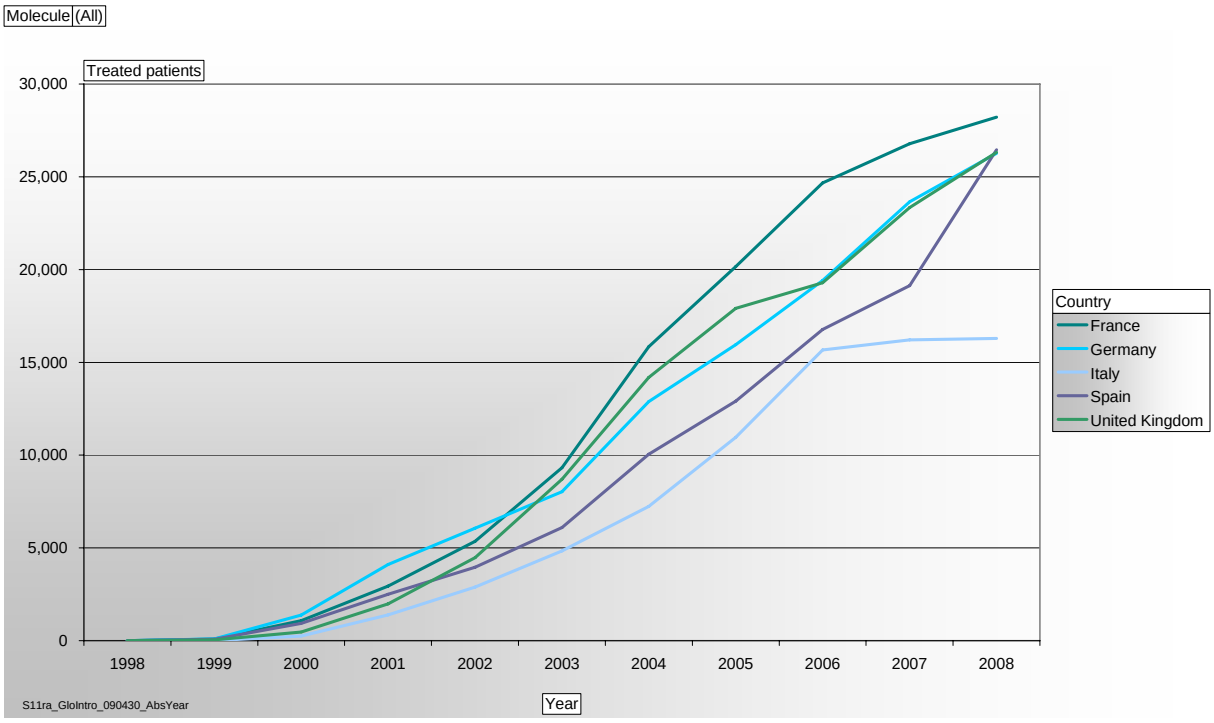
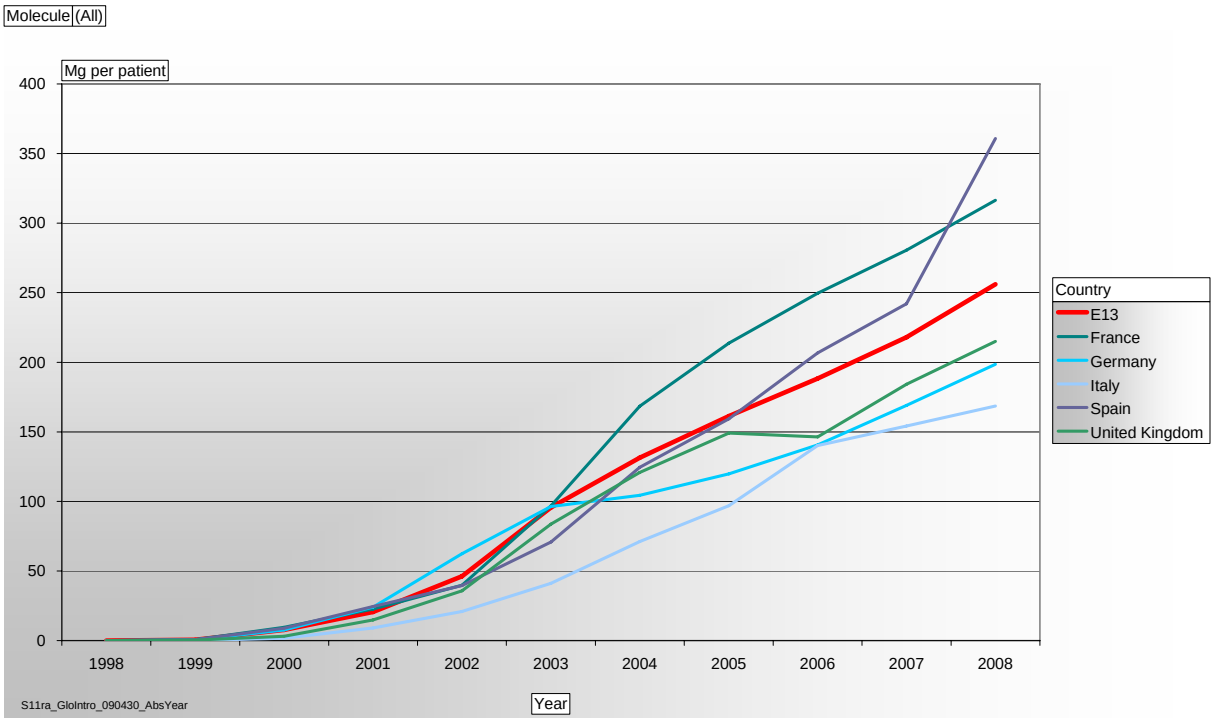
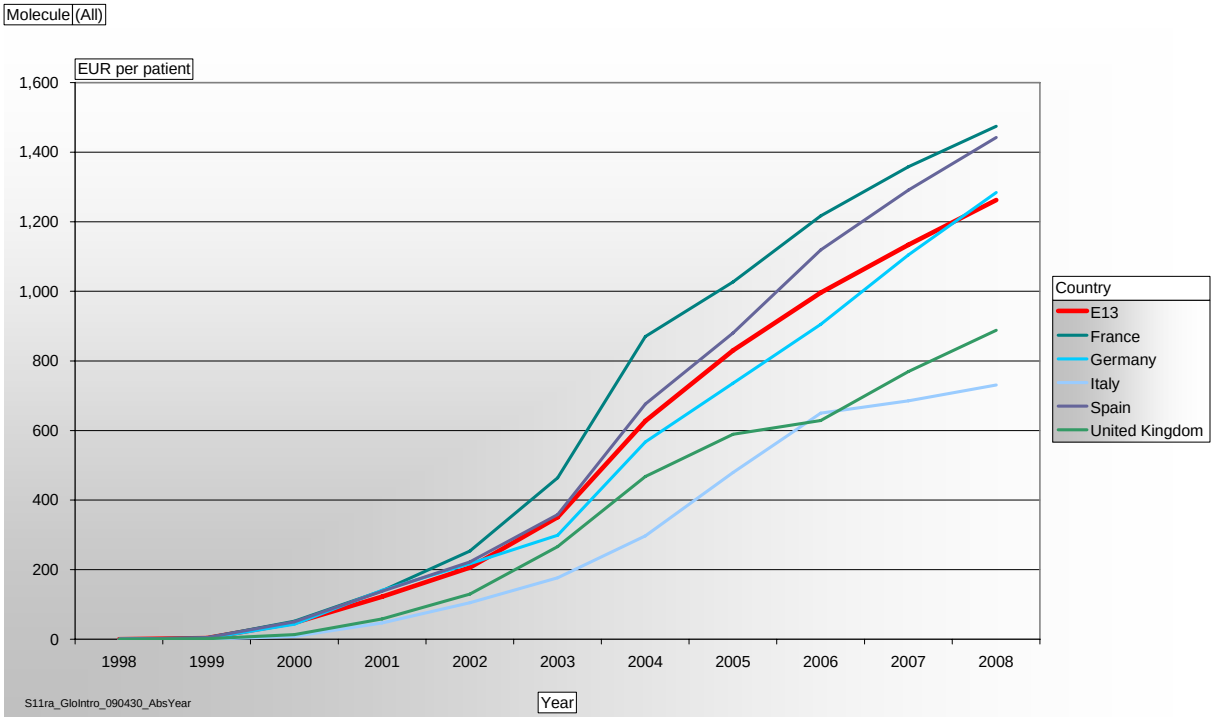


Figure 3-4 Estimated drug quantity per prevalent patient (5 large markets)



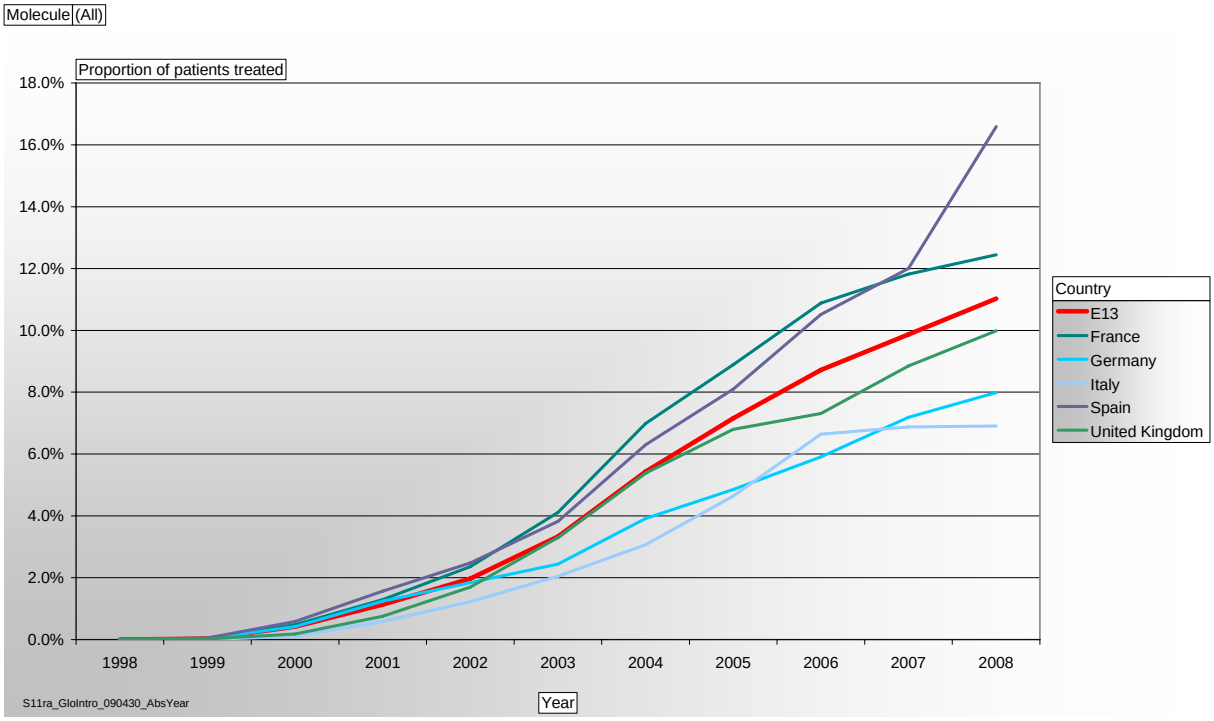
E13 = Western European markets

Figure 3-5 Estimated annual sales (€ 2008) per prevalent patient (5 large markets)



E13 = Western European markets

Figure 3-6 Estimated proportion of patients on treatment



** assumes 12 month treatment for all patients*

The 4 types of analyses can be interpreted as follows:

- The absolute number of patients does not provide any comparison, as populations and prevalence differ between countries. However, they provide interesting information for the individual countries.
- Estimated mg per patient allow a first unbiased comparison between countries. However, as the annual mg quantities differ between drugs, the comparison would have to assume that market shares of the individual drugs are similar among countries. This does not seem far fetched, if one considers the similarity of the curves to the one presenting the proportion of patients treated (where actual quantities for each drug are used).
- The curves of estimated sales per patient add the price dimension to the quantities per patient. This can be illustrated with the examples of Germany, Italy and the UK
    - Germany has a low mg usage and low proportion of patients treated, but the sales per patient are closer to the average due to the higher manufacturer price in Germany.
    - In Italy, mg usage and the number of patients on treatment are low, but so are sales per patient, as a consequence of the low price.
    - In the UK, mg usage and proportion of patients on treatment are close to the European average, but sales per patient are low, as a consequence of the currency fluctuation (depreciation of the GBP against the € in 2008.
- The proportion of patients on treatment provides in our view the best comparison between countries, although they are obviously heavily influenced by the prevalence estimates used.

A further influence on all of these curves comes from our assumption of the proportion of each drug sold in the indication RA.

3.3.2.2 *Nordic Area, Ireland*

Figure 3-7 Estimated total number of patients treated (Nordic Area)

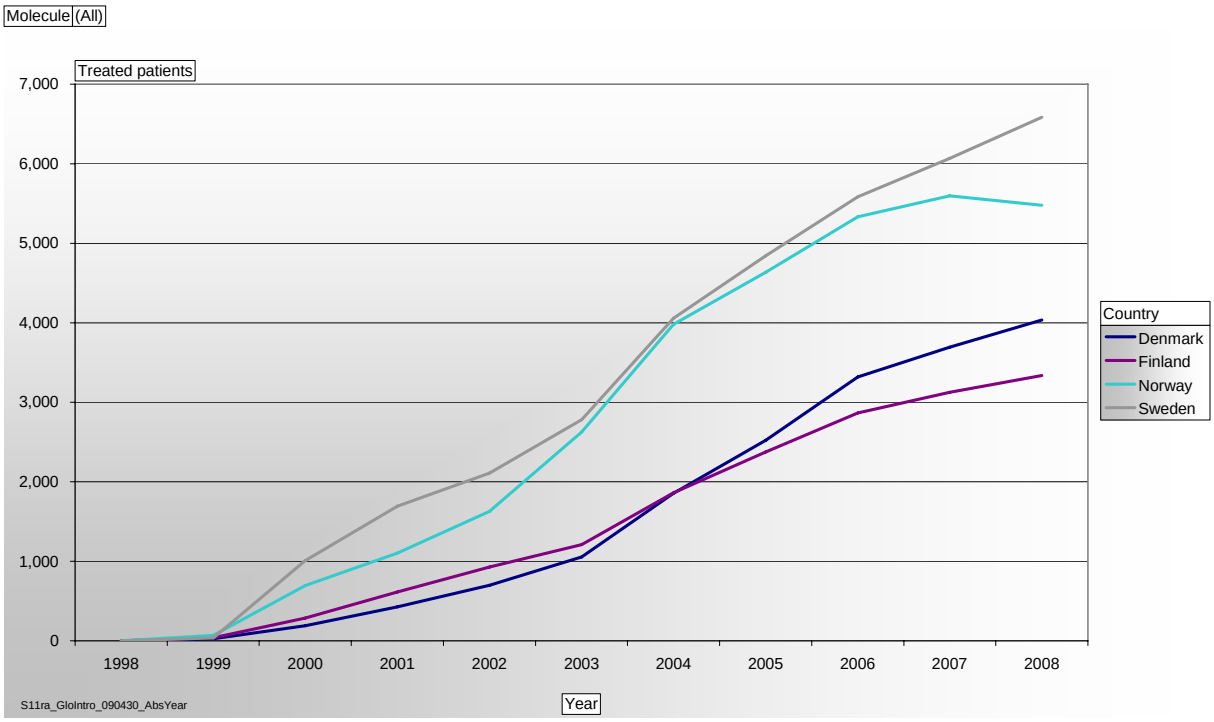
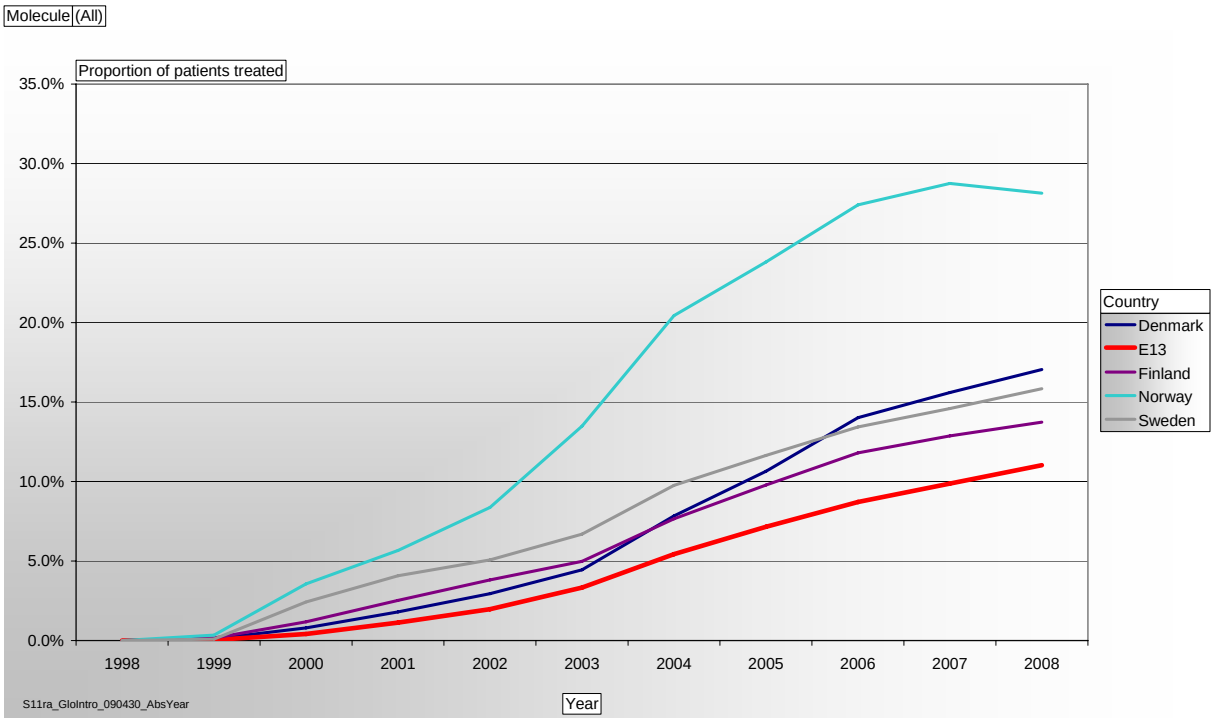


Figure 3-8 Estimated proportion of patients on treatment (Nordic Area)



3.3.2.3 *Small Western European Countries*

Figure 3-9 Estimated total number of patients treated (small W.European markets)

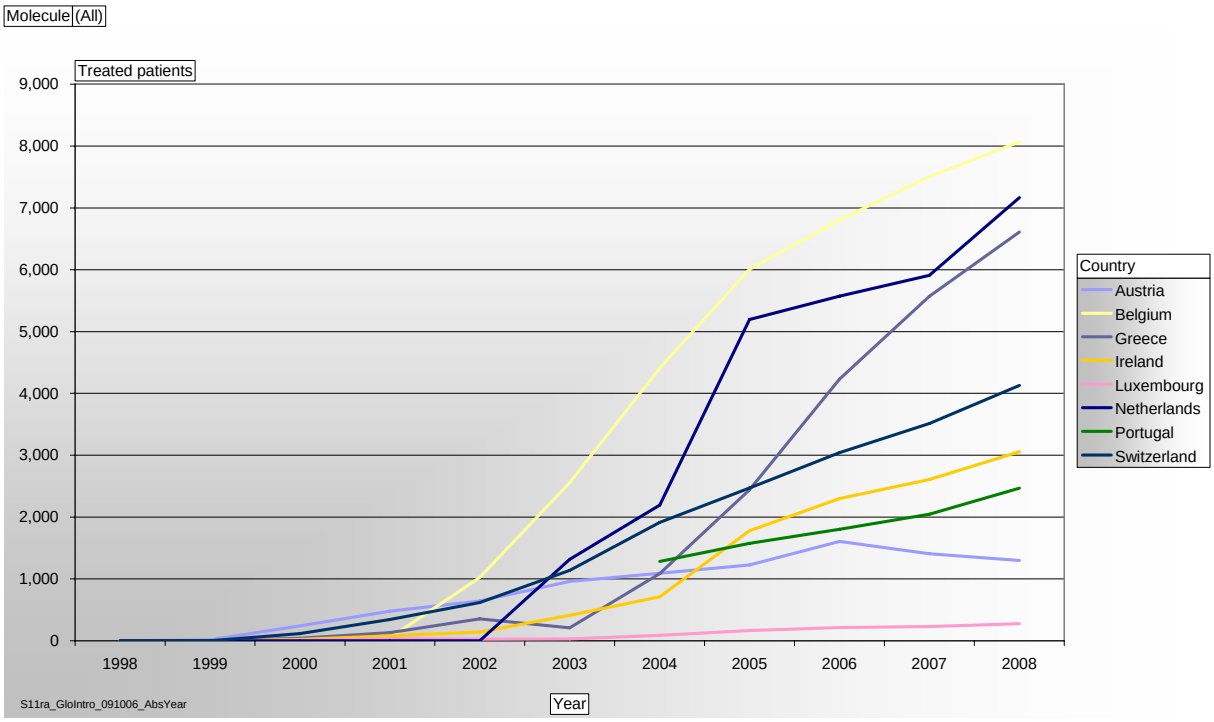
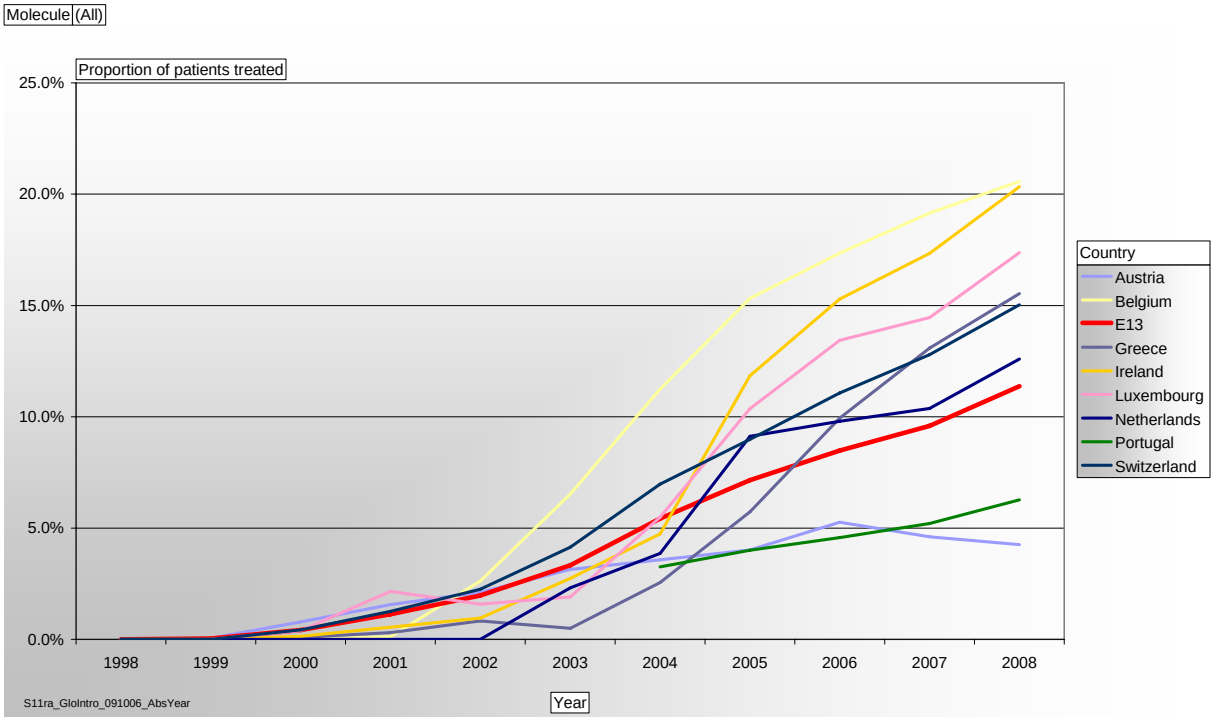


Figure 3-10 Estimated proportion of patients on treatment (small W.European markets)



3.3.2.4 *New EU member states*

Figure 3-11 Estimated total number of patients treated (selected new EU countries)

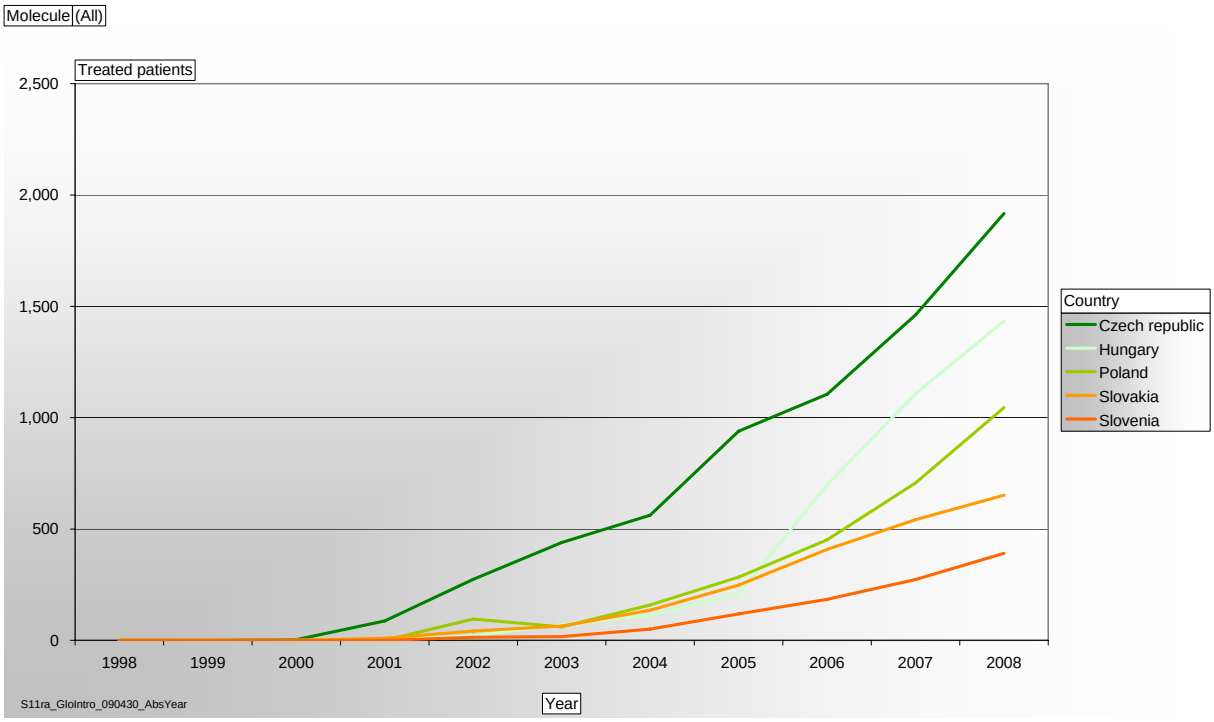
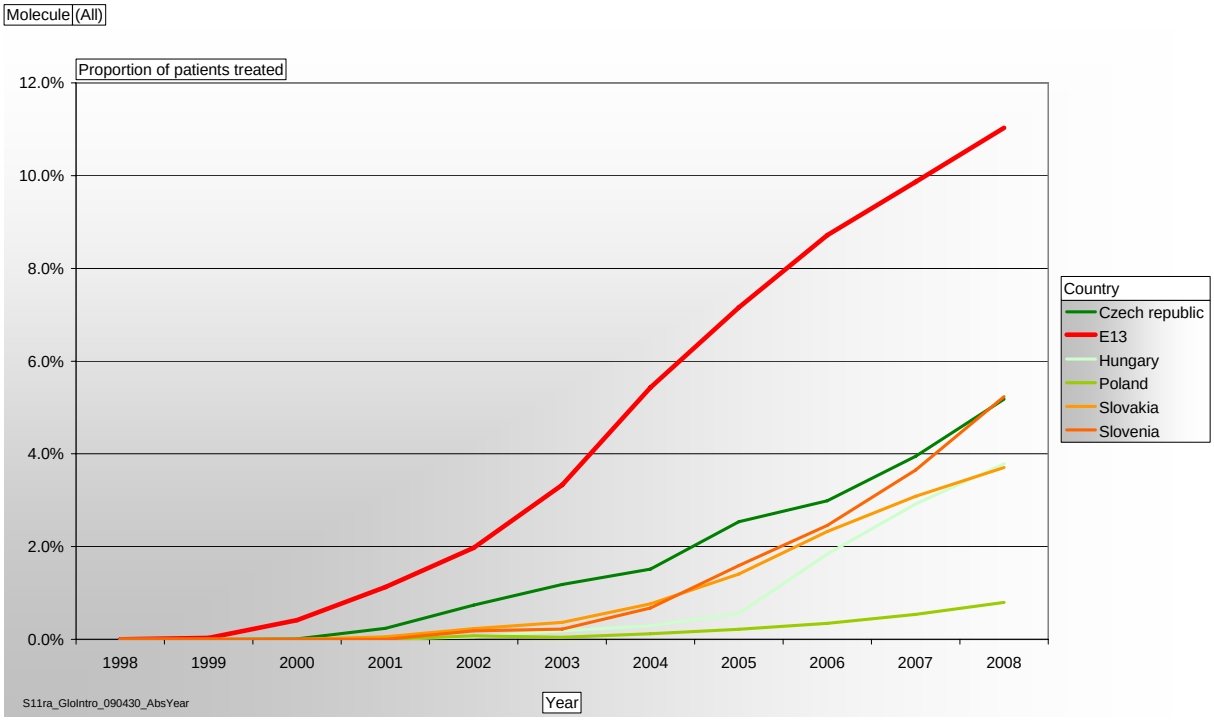
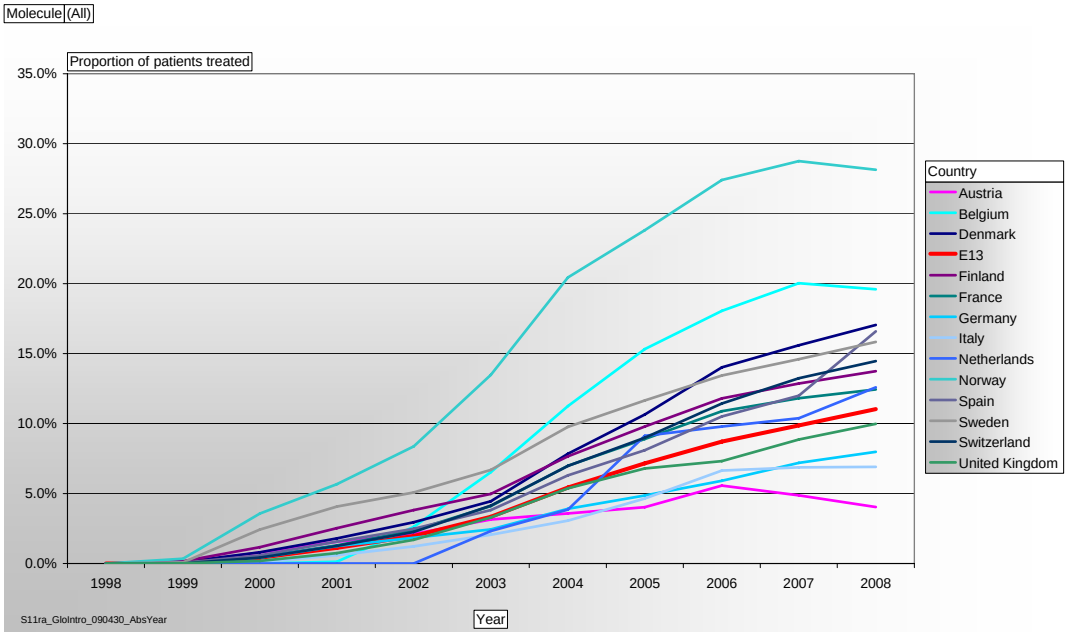


Figure 3-12 Estimated proportion of patients on treatment (selected new EU countries)



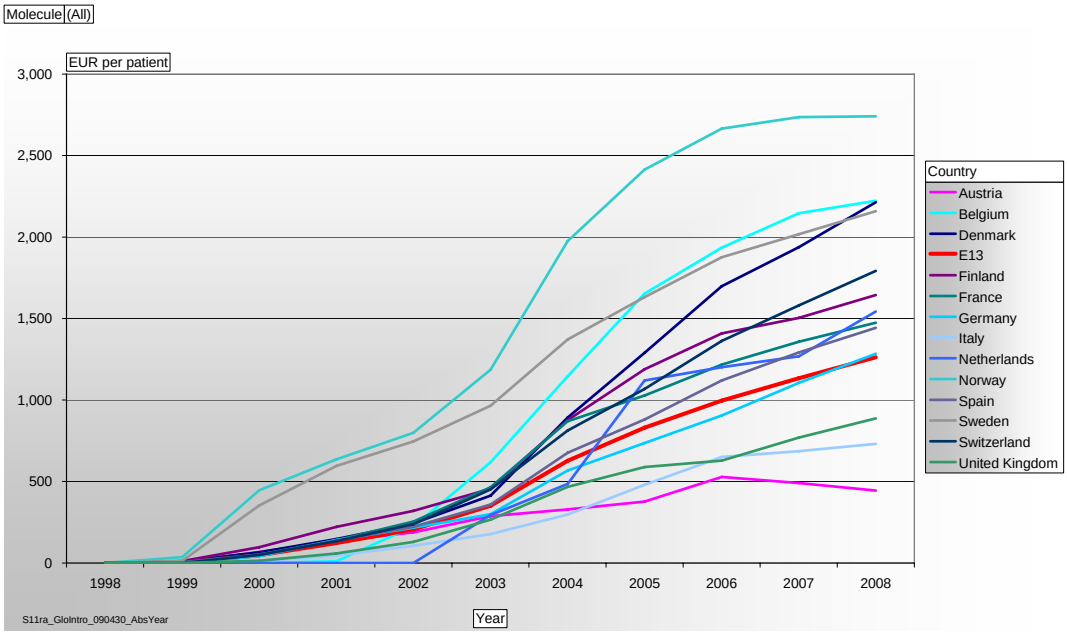
3.3.2.5 *Comparison of E13 countries*

Figure 3-13 Proportion of patients on treatment in E13 countries



The clear front-runner is Norway, followed by Belgium, Switzerland and Sweden, while Austria, Italy, Germany and the UK provide access below average to their patients. When looking at sales per patient, the picture is similar, with the exception of Germany where the influence of the higher price and the UK where the depreciation of the Pound can be observed.

Figure 3-14 – Sales per patient (€ 2008), E13



3.3.2.6 *Analysis by Drug – 5 Large Markets*

An analysis of usage by drug in the 5 large markets does not reveal any further differences for the 3 TNF-inhibitors. France and Spain not only treat most patients, but they also are the largest users of all drugs. Abatacept is more difficult to interpret, due to its recent introduction.

Figure 3-15 Proportion of patients treated with different drugs (etanercept)

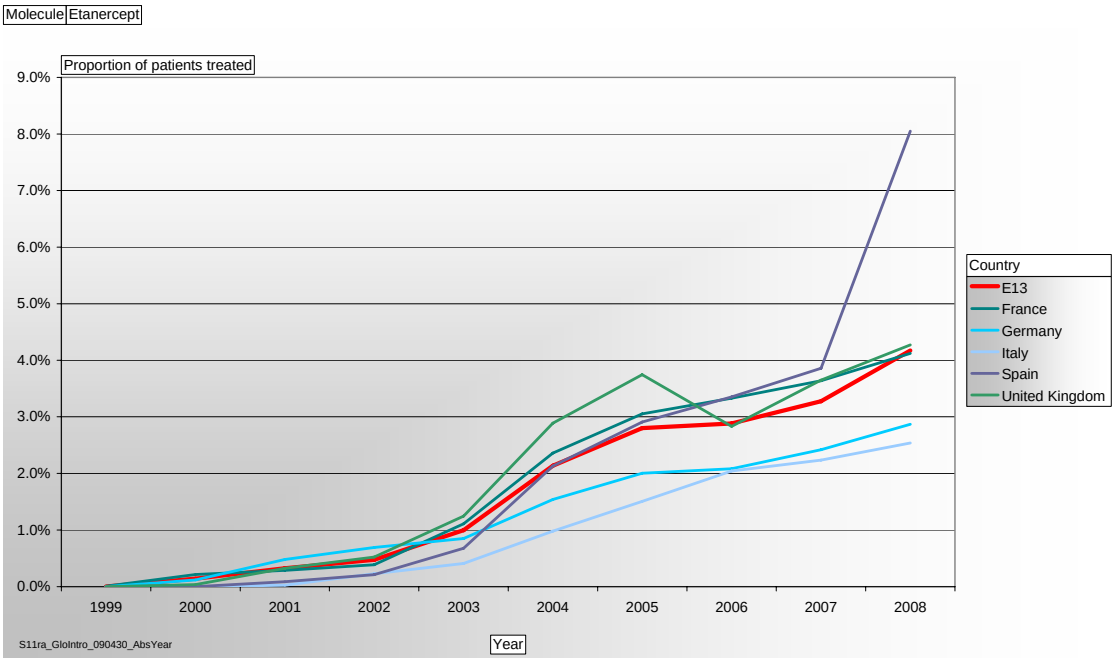


Figure 3-16 Proportion of patients treated with different drugs (infliximab)

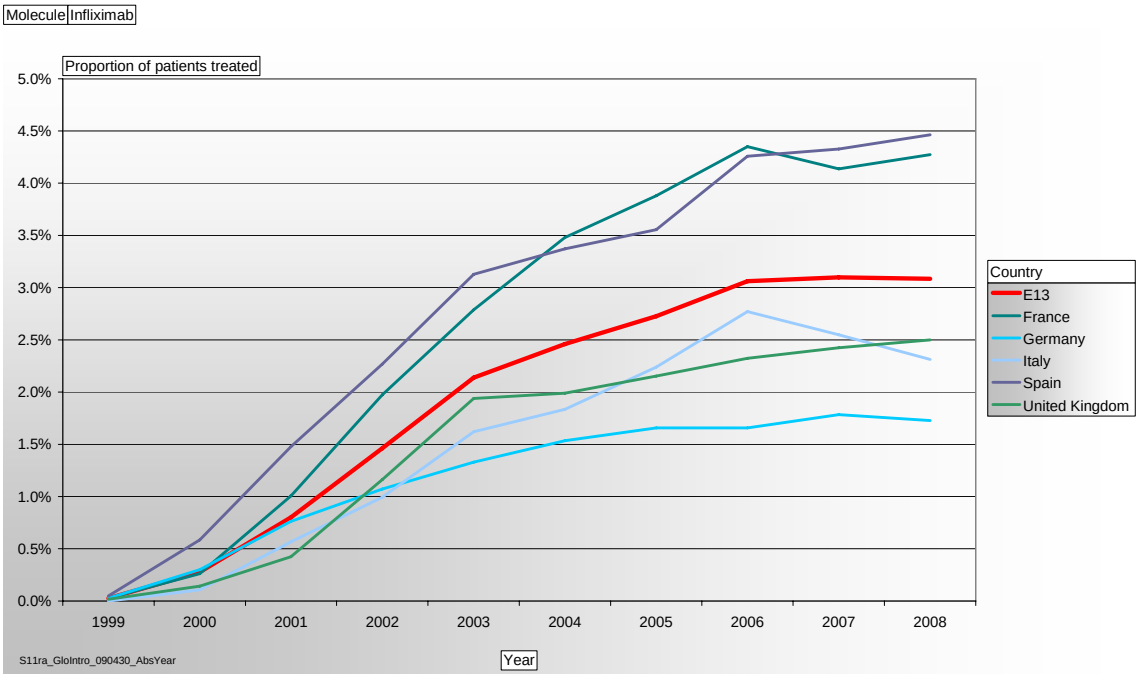


Figure 3-17 Proportion of patients treated with different drugs (adalimumab)

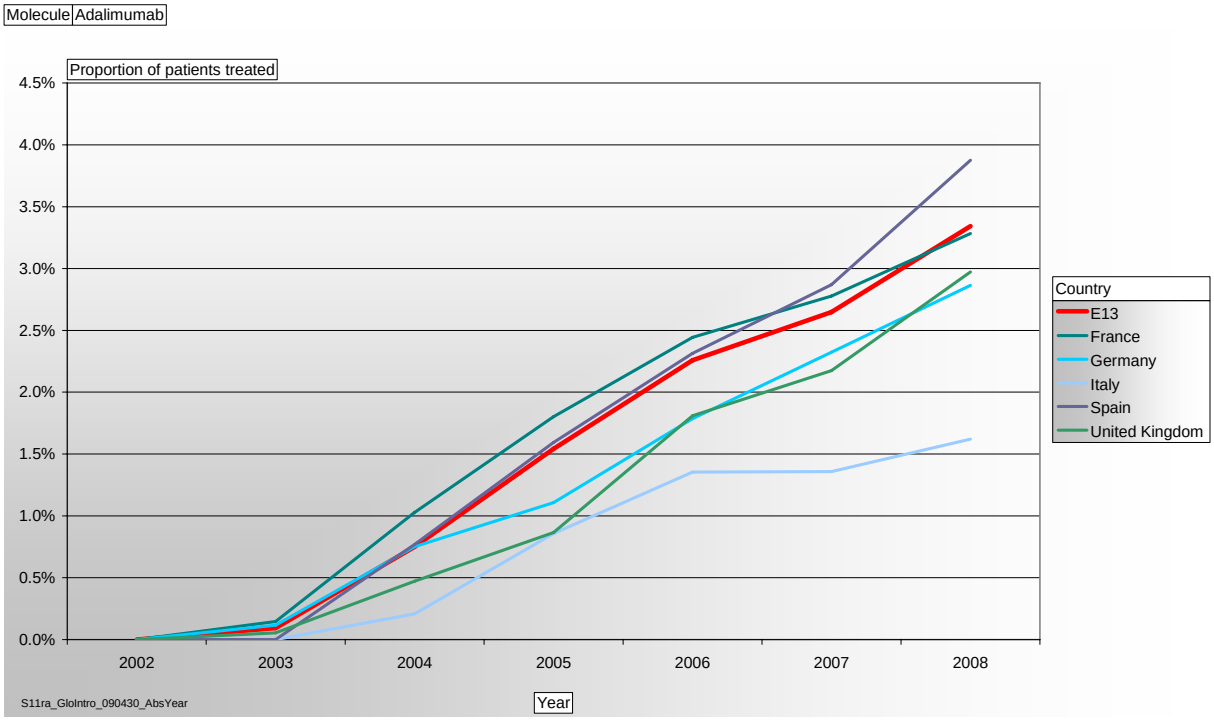
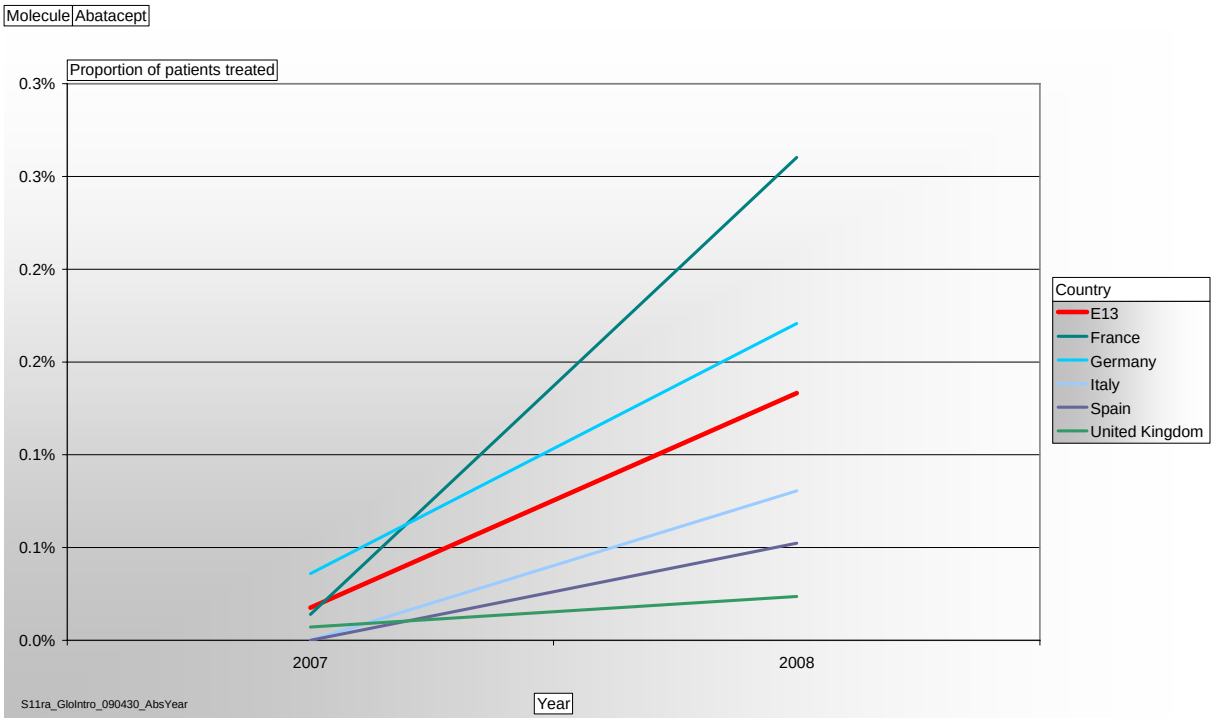
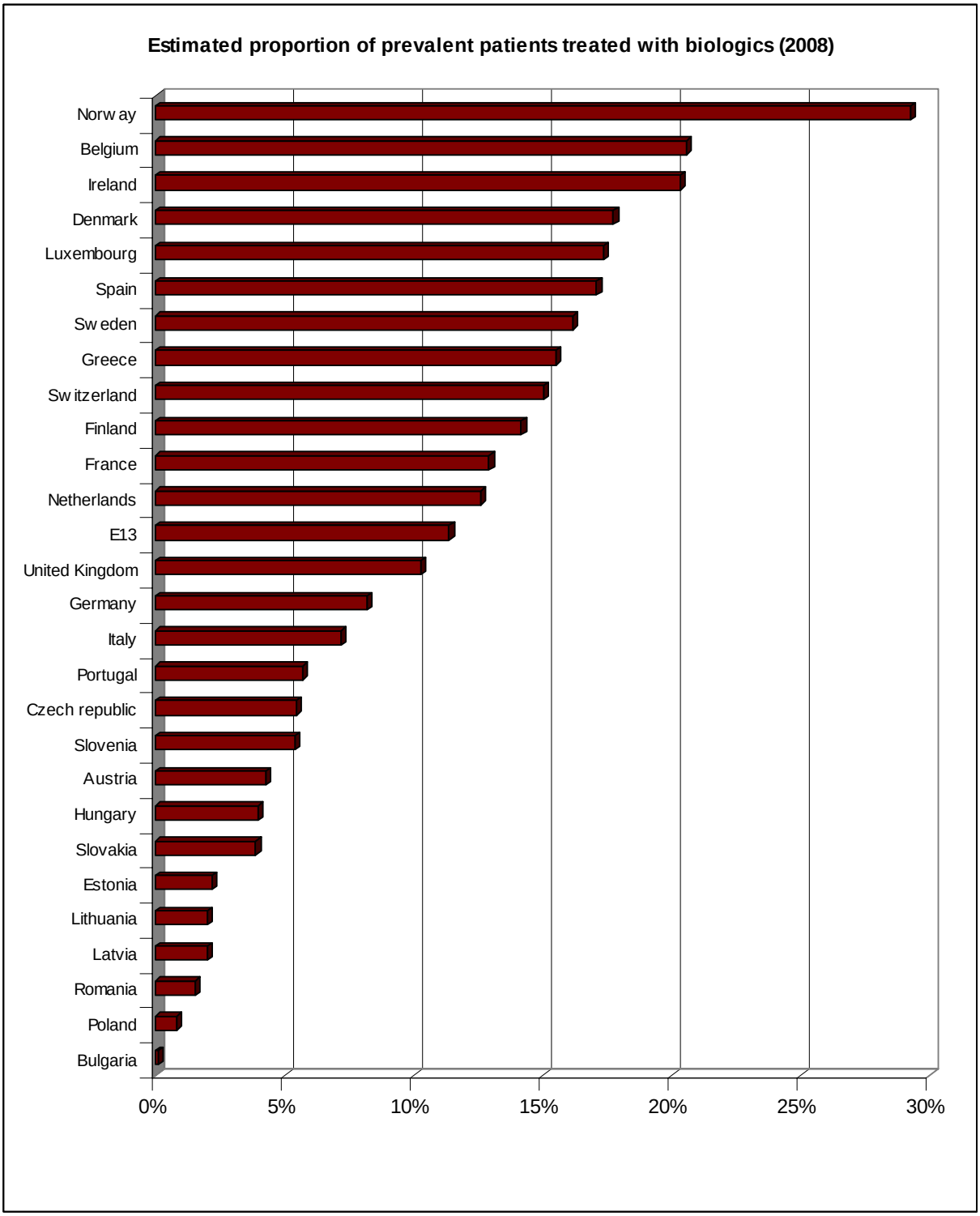


Figure 3-18 Proportion of patients treated with different drugs (abatacept)



3.3.2.7 *Proportion of patients treated across Europe*

Figure 3-19 Proportion on treatment end of 2008



For these calculations, we have used our own prevalence estimates. A recent report by the Innovative Medicines Initiative (IMI, Strategic Research Agenda) used substantially higher prevalence rates for Germany and the United Kingdom, while numbers for France, Spain and Italy were consistent with our estimates. If we were to apply these rates to Germany and the United Kingdom (0.9% and 0.88% in the population over 15), utilization rates would drop considerably. The proportion of patients treated in Germany would stand at 4.6% and in the United Kingdom at 6.9%. We believe that this would underestimate use particularly in Germany, where the prevalence data are not supported by any study but are implied from rates used in studies from the 80s and early 90s.

3.4 Conclusion

In order to compare access to biologic drugs in Europe in the absence of actual data on the number of patients on treatment, the following information is required:

- prevalence data
- sales data
- drug prices
- proportion of sales within the indication of interest.

Neither of these datasets was readily available, and we have based our estimates on the following methods:

Prevalence has been re-estimated using age and gender adjusted patient level data in 2 countries. Sales data were available both as quantity and cost from IMS, and with a number of adjustments, these data have been used. We have also derived the manufacturing price from the IMS data set; end-user prices were not used, as biologics are distributed through special channels in many countries and wholesale and pharmacy margins can not be applied. Finally, the proportion of sales for RA for the different drugs was not available neither from IMS nor the manufacturers and we have made our own estimates.

Drug uptake presents the expected influence of the economic wealth of European countries, but also differences between similar countries that cannot be explained easily and are explored in the next chapter.

Chapter 4 - Determinants of Access

CONTENT

4 Determinants of access to treatment in RA
- 4.1 Summary 4-2
- 4.2 Introduction....4-3
- 4.3 Affordability 4-3
- 4.4 Patient Eligibility....4-8
- 4.5 The reimbursement process 4-8
- 4.6 Treatment guidelines....4-10
- 4.7 Price 4-11
- 4.8 Budgets 4-11
- 4.9 Health technology assessments 4-11
- 4.10 Health economic studies in RA....4-13
- 4.11 Access to medical care 4:16
- 4.12 Conclusion....4:18
- 4.13 References 4:18

TABLES

Table 4-1 Comparison of prices, health expenditures and ability to afford 4-4
Table 4-2 Eligibility criteria for access to biologics and related use 4-10
Table 4-3 – Published cost-effectiveness analyses 4:15

FIGURES

Figure 4-1 Price comparison across countries (Germany=100)*.....4-5
Figure 4-2 – Comparison of health expenditure/capita (Germany=100) 4-6
Figure 4-3 – Affordability Index (Germany = 100) 4-7
Figure 4-4 – Patients W.A.I.T. Indicator 4-9
Figure 4-5 Studies on costs, patient outcomes and cost-effectiveness in HEED related to RA between 1990-2008 4-13
Figure 4-6 Number of patients with RA per rheumatologist 4:17

4 Determinants of access to treatment in RA

4.1 Summary

An important determinant for access and strong reason for restrictions in the use of the biologic treatments has been their cost and impact on health care budgets. This chapter discusses the importance of economic factors in the reimbursement and prescription of biological treatments for RA patients, as well as other factors that influence usage and lead to differences among markets

The largest differences in access are the consequence of a global price for the drugs and large differences in wealth and hence affordability among countries in Europe. The relationship between GDP, expenditures on health and global drug prices leads to a large difference in affordability between Western Europe and the new EU member states.

However, health technology assessment studies and economic evaluations also have to be seen in front of this background. A treatment at a price between €10-15,000 will lead to different cost-effectiveness results in countries where the average total annual cost for a patient ranges from €500 for patients with early and mild disease to €5,000 for patients with advanced severe disease than in countries where this range is between €3,500 and €35,000.

While there appears to be no doubt concerning the effectiveness of these drugs, different countries have had different views on how cost-effective they are. Countries such as Norway and Sweden have found the TNF-inhibitors to be good value for money, with the result that they are currently among the top 10 drugs on the drug budget. Other countries such as e.g. United Kingdom have evaluated them less favourably and usage is more restricted.

Beyond the economic factors, access to treatment is defined by medical practice, i.e. clinical guidelines, but also the ease of access to care and availability of care. For instance, some countries lack rheumatologists while others have lengthy referral processes to specialists that both can lead to long waiting times for consultations and hence late diagnosis and treatment. Other factors that influence usage are, among others, prior approval requirements, limitations in prescribers of biologics and institutional or practice budget limitations or caps.

No one of these factors in isolation explains the differences in uptake of biologics between European countries. General economic conditions explain to a large extent the big difference between Western and Central/Eastern European countries. However, differences between countries with similar economic conditions are explained by a combination of economic organisational factors as well as clinical practice.

4.2 Introduction

RA drugs are to a large extent used in an outpatient setting. In countries with a public reimbursement for drugs, this means that inclusion in the reimbursement system is a very important criterion for funding of, and access to, the treatments. The reimbursement systems for drugs and the criteria for reimbursement have seen a rapid change in many countries during the last two decades, with costs and value for money becoming more important factors for reimbursement. Cost-effectiveness has emerged as an additional criterion to fulfil before a new drug reaches the market, alongside clinical safety, efficacy, effectiveness and quality that are requirements for marketing approval by the EMEA and national Medicine Agencies.

The introduction of biological drugs for the treatment of RA in recent years constitutes an example of the role played by economic considerations for patient access to innovative but expensive treatments. As shown in chapter 4 in this report, between 9-10% of all RA patients in European countries are treated with biological drugs. (This estimate uses our prevalence estimates from chapter 1, where patients are defined as those with a definite diagnosis and regularly followed, i.e. with more than one health care contact with this diagnosis.) The variation is however high, with a range from 1% or less in Bulgaria to almost 30% in Norway:

- In Western Europe (old EU plus Iceland, Norway Switzerland), we estimate average usage at 11-12%, with a range from less than 5% in Austria and close to 30% in Norway. The 3 large markets of Germany, Italy and the United Kingdom have a usage below 10% and drive the mean values; excluding them yields an average use in 15% of the patient population in Western Europe.

- In Central and Eastern Europe (new EU member states) the estimate is around 2%, with a range <1% in Bulgaria to 5-6% in the Czech Republic and Slovenia.

This difference is essentially related to the different wealth (GDP) in the different parts of Europe. Drugs are competing in a global market, and in particular in the EU with free movements of goods, they are priced within a narrow price band to avoid parallel trade. This de facto makes it difficult for countries with a lower GDP to afford treatments such as the biologics used in RA and creates large differences in access.

4.3 Affordability

For this analysis, we first established relative prices and relative expenditure per capita, using Germany as an index of 100 in both cases. Comparing the two provides an index on how well biologics at the given price can be taken up within the health care budget. A higher index indicates more difficulties to afford.

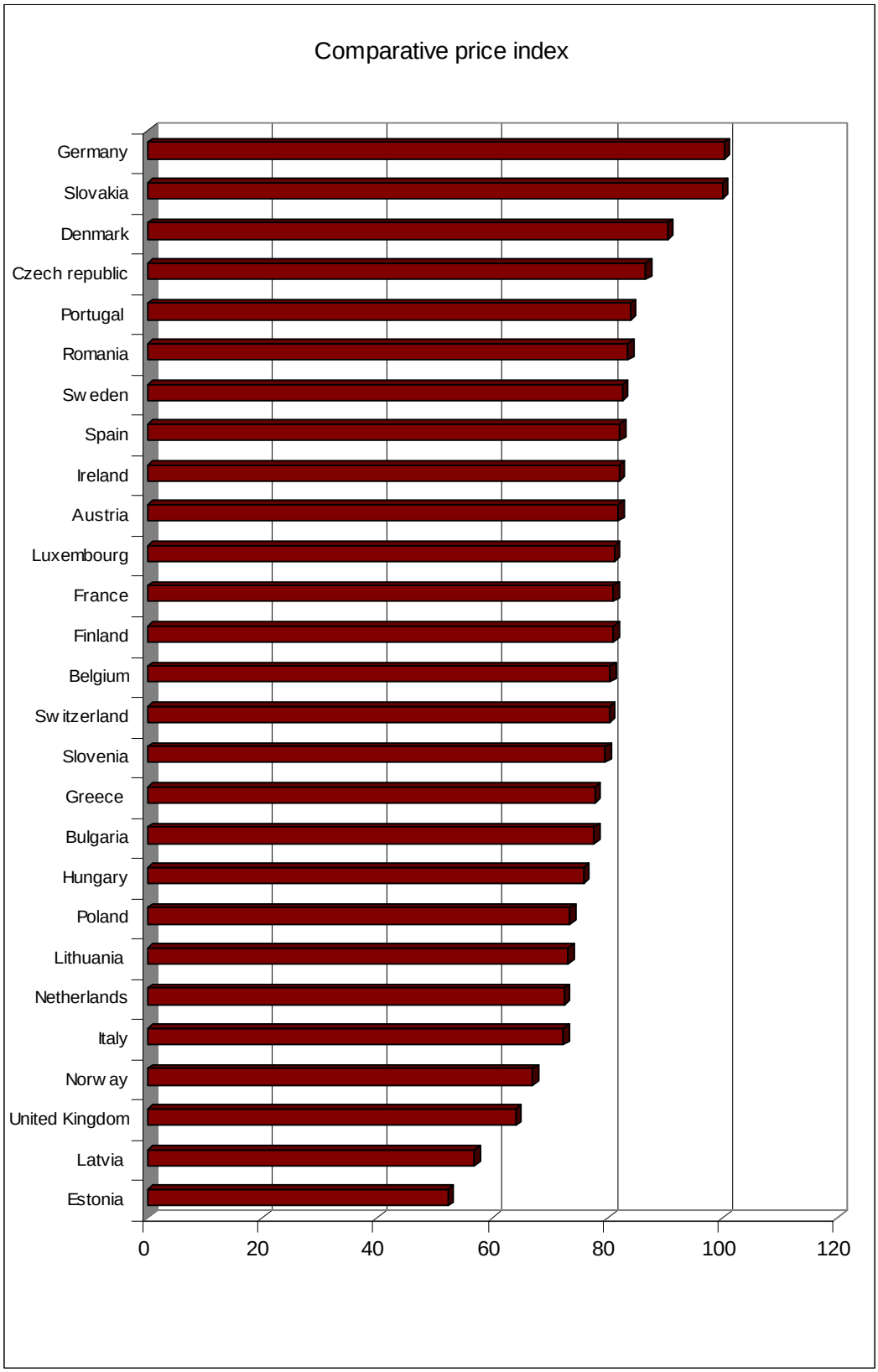
However, we have arbitrarily reduced the German price by 5%. Until spring 2009, manufacturers could distribute biologics directly, thus avoiding the wholesale and pharmacy margin. Some of this distribution cost has likely been incorporated into the ex-factory price, but no detailed data are available, neither on the exact mark-up and for which product this would apply. We have therefore decided to reduce the ex-factory price by about half the wholesale margin in 2008.

Table 4-1 Comparison of prices, health expenditures and ability to afford

Country	TNF price index [1] Germany = 100	Relative health expenditure/capita [4] Germany=100	Affordability index [6]
Austria	82	107	77
Belgium	81	103	79
Bulgaria	78	28[5]	278
Czech republic	87	45	193
Denmark	90	100	90
Estonia *(uncorrected)*	52[2]	31[5]	169
Finland	81	79	102
France	81	102	79
Germany	100	100	100
Greece *(retail)*	78	74	105
Hungary	76	45	169
Ireland	82	91	90
Italy	72	78	93
Latvia *(uncorrected)*	57[3]	30[5]	190
Lithuania *(uncorrected)*	73	25	294
Luxembourg	81	180[5]	45
Netherlands	72	94	77
Norway	67	134	50
Poland	73	27	271
Portugal *(hospital)*	84	63	133
Romania	84	19[5]	440
Slovakia	100	39	257
Slovenia	80	64[5]	126
Spain	82	73	113
Sweden	83	95	87
Switzerland	80	128	62
United Kingdom	64	82	78

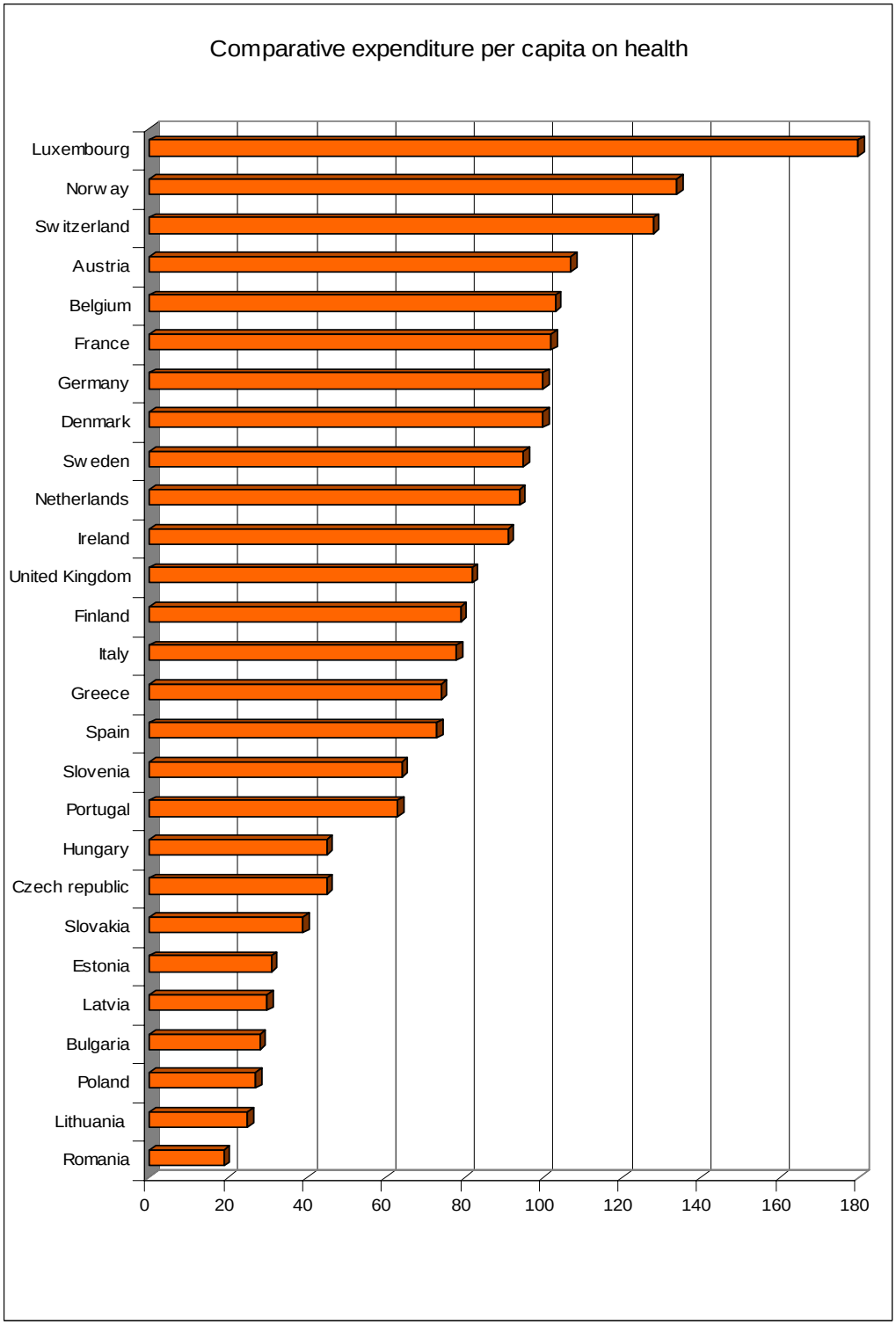
1) *Price index based on un-weighted average of the 3 TNF inhibitors Germany = 100*
2) *Data for only 1 product*
3) *Data for 2 products only*
4) *Source: OECD Health Data 2008*
5) *Source: WHO statistical information system, 2006 adjusted*
6) *Calculated comparing the index of health care expenditures to the price index. Higher indexes indicate lower affordability.*

Figure 4-1 Price comparison across countries (Germany=100)*



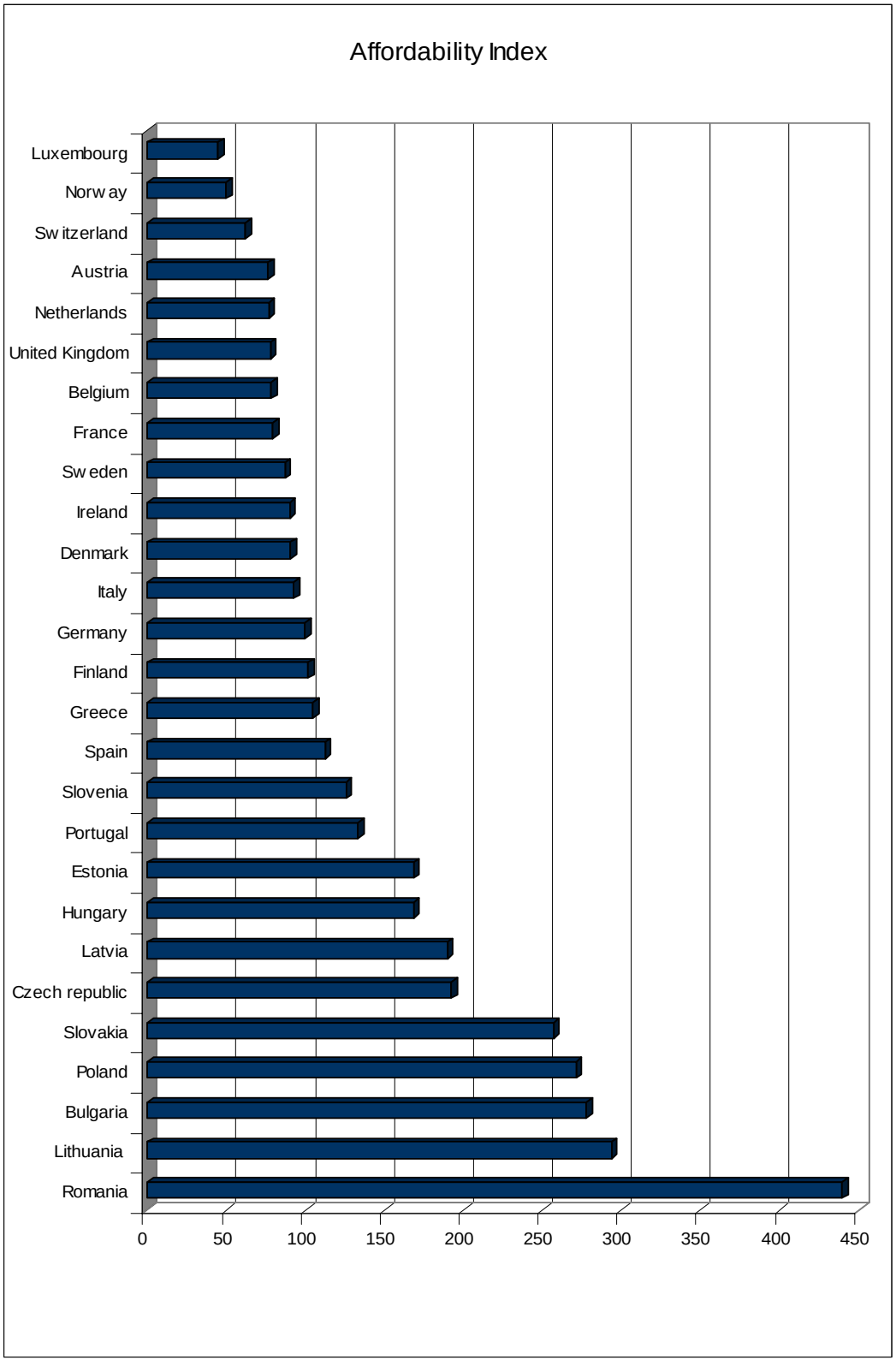
**TNF inhibitors only, unweighted ex-factory prices*
(Note: only infliximab available in Estonia)

Figure 4-2 – Comparison of health expenditure/capita (Germany=100)



Source: OECD Health Data 2009, WHO Health Statistics

Figure 4-3 – Affordability Index (Germany = 100)



Comparison of health expenditures per capita (index) to the price of biologics (index). Low indexes indicate good affordability, high indexes indicate difficulties to afford.

4.4 Patient Eligibility

Different bodies have provided different estimates on the number of patients that would benefit from treatment with biologics. Many of these estimates were made at the introduction or during the early use of these drugs, and therefore likely influence by initial caution regarding their adverse event profile. In addition, they were obviously influenced by the restrictions that were put in place by payers to limit the budget impact, and different levels of restrictions hence translate in different estimates of the patient population eligible for biologics, illustrated with two examples below.

In 2001, Douglas et al estimated that under the criteria established by the British Society of Rheumatology (BSR) in 1999, an estimated 6-7% of patients might be eligible for biologic treatment [1]. Using a general formula of 10% of patients having severe diseases, and 20% of these would be eligible for biologic treatment yielded an even lower estimate (2%). Guidelines for biologic treatment of the BSR are currently in revision, but the eligibility criteria do not appear to have changed (draft available at http://www.rheumatology.org.uk/guidelines). Yet, according to our estimates, biological treatment is provided to 10% of patients using our prevalence estimates from chapter 1. Using the somewhat higher overall prevalence estimates by Symmons of 0.8% [2], an estimated 7.5% of patients would be on biologic treatment.

As a comparison, the Danish National Board of Health estimates that 10-20% of patients that are treated by a rheumatologist are no longer getting any benefit from classical DMARDs and would benefit from treatment with TNF inhibitors [3]. In our estimates, 17-18% of patients are currently treated with biologics in Denmark.

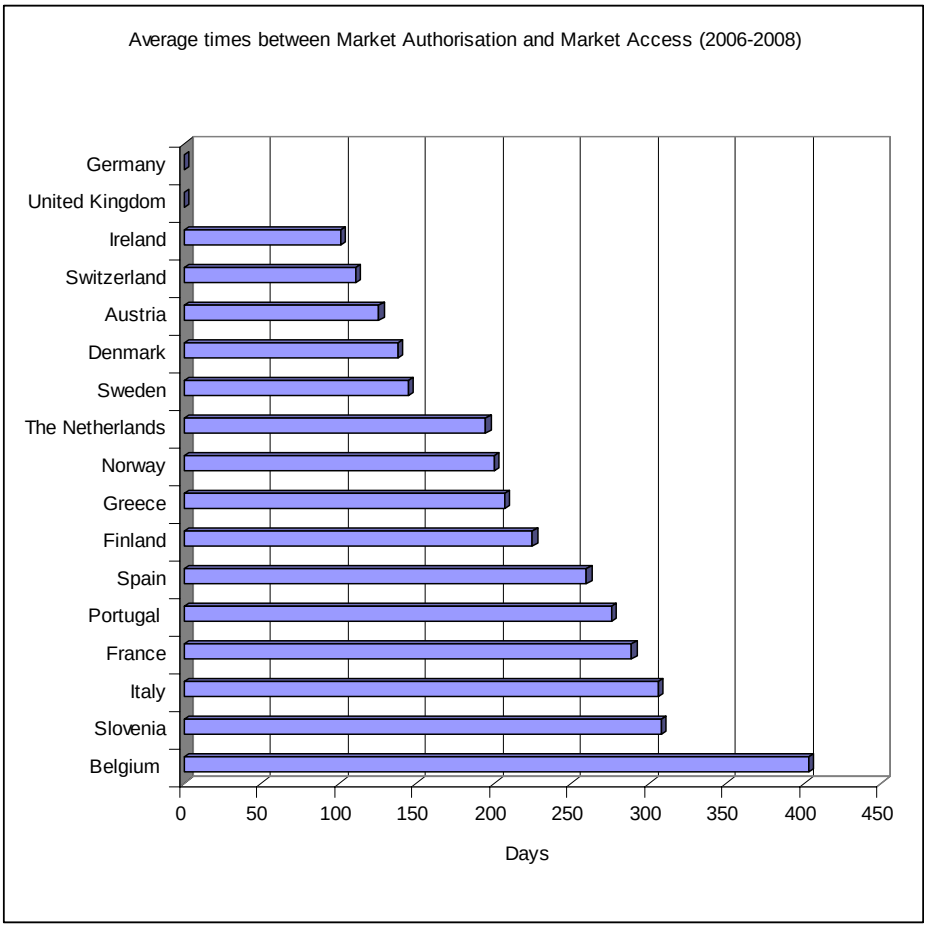
This estimate of 10-20% eligible patients appears currently well accepted. It is, however, based on current guidelines and restrictions (see below). It does thus not take into account the more recent findings of a short therapeutic window particularly in severe erosive disease where structural damage can be observed already within 3-6 months after first symptoms. It is virtually impossible to implement biologic treatment within this time frame in most countries, as it would mean reducing both the number of DMARDs that patients have to have failed on, and the time during which these need to be evaluated. Doing so, in the absence of perfect prognostic criteria, will increase the number of eligible patients, and payers may be reluctant to fund biologics for larger patient populations.

4.5 The reimbursement process

Most countries have formal mechanisms for making national reimbursement decisions, with the exception of Germany and the United Kingdom where no specific decisions have to be made before a drug can be prescribed under the reimbursement system.

The reimbursement process can take more or less long, depending on the country and also on the technology in question. As an indication, we show below preliminary results of the 2009 "Patients W.A.I.T. Indicator" produced by IMS Health based on EFPIA's database on first marketing authorisation in the period 2006-2008. Compared to the 2008 indicator, little has changed. The delay from EMEA authorisation to completion of the reimbursement process in 15 European countries (excluding Germany and the United Kingdom) varies from 101 to 403 days, compared to 98 to 412 days in the previous report.

Figure 4-4 – Patients W.A.I.T. Indicator



In Belgium, Finland, the Netherlands, Norway, Portugal and Sweden there is a formalized decision-making process where economic evaluation and the issue of cost-effectiveness play an important role. In France, Italy and Spain, cost-effectiveness information is used as additional information for pricing and reimbursement decisions, although not as formally as in the countries above. For Denmark and Switzerland the role of economic evaluation and cost-effectiveness is not a formalized part of the decision-making process. The UK has no formal restriction for pricing and reimbursement of drugs, but the government still controls the pricing and can, for example, require price cuts and paybacks from companies. A number of Eastern European countries have also recently introduced economic evaluation into their reimbursement process (e.g. Hungary, Poland, Czech Republic, and Lithuania) [4].

Within these processes it is sometimes possible to define the eligible patient populations more restrictively than in the market access authorisation by the EMEA, although actual control mechanisms are lacking in most countries. However, in the field of biologics in RA, clinical guidelines have to some extent played this role, with the objective to ensure access for patients with the highest medical need without creating issues for funding.

4.6 Treatment guidelines

Market authorisation and reimbursement of drugs does not ensure their utilisation. For most diseases there are a number of reimbursed drugs to choose between, and treatment recommendations/guidelines form important guidance for physicians in many countries. Such information may be provided at national or local levels.

Most countries have issued new clinical guidelines for treatment of RA, or updated existing ones, to incorporate usage of the biologics. The main objective for this was to use these potent but costly treatments appropriately both from a medical and economic point of view. Most of these documents define rather precisely which patients are eligible for biologic treatment, with TNF-inhibitors being the first option. Since the introduction of further classes of drugs, some of the guidelines also define the sequence in which they should be used (e.g. NICE guidance).

These definitions of eligible patients can be expected to have a strong effect on access within the countries, and thus differences between them. The table below lists the criteria used in different countries (adapted from Emery et al [5]), and relates them to usage estimates in our study. Indeed, countries where the guidelines require a disease activity score (DAS28) of more than 5.1, such as Italy and the United Kingdom, usage is lower than average. (For the Czech Republic, the GDP level has an additional influence.) Germany appears to be an outlier: The guidelines are very open, similar to the Danish guidelines, yet Denmark treats twice as many patients with biologics as Germany. Hence, there are other factors that play a role. (Note that the list of guidelines in the paper by Emery is not exhaustive.)

Table 4-2 Eligibility criteria for access to biologics and related use (from [5])

Country	*Level DAS28 required*	*Previous DMARD treatment required*	*Minimum time on previous DMARDs*	*Evaluation of effect*	*Estimated use of biologics*
Belgium	-	2, 1 one of them MTX	6 months in total	3-6 months	20.6%
Czech Republic	**>5.1**	2, 1 one of them MTX	6 months each	3 months	**5.4%**
Denmark	Persistent synovitis in ≥6 joints	2, 1 one of them MTX	4 months each	4 months	17.7%
France	>5.1 >3.2 despite of corticosteroids	1	3 months	-	12.9%
Germany	-	2, 1 one of them MTX	6 months in total	3 months	8.2%
Italy	**>5.1**	2, 1 one of them MTX	3 months each	3 months	**7.2%**
Spain	>3.2	- 1 - 0 in case of aggressive disease	4 months	4 months	17.1%
Sweden	>3.2	- 2, 1 one of them MTX - MTX only in case of aggressive disease	2-3 months total	2-3 months	16.2%
United Kingdom	**>5.1**	2, 1 one of them MTX	6 months each	3 months	**10.3%**

DAS28 = Disease activity score, 28 joints; MTX = methotrexate

4.7 Price

The cost of biologics clearly influences their usage, with most health care payers defining more or less restrictively the subgroups in which they can be used, in part depending on the wealth of the country. A part from the macroeconomic conditions in the countries, prices have a poor explanatory value for differences in uptake between the countries. Indeed, ex factory prices are within a narrow price band. The actual public prices for all drugs in each country were not easily available, as in many countries special distribution channels are used and some of the products are hospital products, and normal margins do not apply. We have therefore used manufacturing prices for the comparisons presented in the previous chapter.

In the table above, Germany and Italy have the lowest use of biologics in Western Europe. Germany has the highest ex-factory price in Europe, while Italy has one of the lowest, and it is unlikely that this difference is made up by margins (see chapter 4 Figure 4-3). Hence, while the high price in Germany may explain some restraints in usage, the low price in Italy does not. For these countries, organizational issues in the health care financing such as budgets are a better explanation of the differences than price.

Some of the recent currency shifts versus the Euro have "disturbed" the price band. During 2008, the Norwegian Krona and in particular the British Pound have depreciated against the Euro and biologics in these countries have therefore comparatively low prices in Euro, despite being countries with traditionally high pharmaceutical prices. During 2009, this has also been the case for the Swedish Krona, but this does not affect our data that include the time up to end of 2008. The effect of these currency changes will be an increase in parallel export. Parallel import occurs currently particularly into Germany, from several countries, as a consequence of the high ex-manufacturing price. However, the influence on usage is likely limited, as in fact a minor part of the difference reaches the end-user.

4.8 Budgets

A number of countries, but also regions and even hospitals have special budgets or budget controls for biologic drugs, but these details are beyond the scope of this report.

The consequence of budget controls can however be illustrated for the two countries discussed above, Germany and Italy, as it clearly appears to affect usage. Both have budgetary restrictions: Germany has fixed practice budgets for doctors, and excess spending is claimed back from the treating physician by the payers, unless the patient population can justify the extra expense. While it is often possible to justify this in the case of RA, it is a priori a hurdle and prescribers are extremely careful. In Italy, biologics can only be prescribed in the hospital setting, and hospital drugs are limited to 2.4% of total spending.

4.9 Health technology assessments

Health technology assessment (HTA) reports published by national or regional HTA agencies often form part of the evidence for treatment recommendations/ guidelines and are by themselves important influences for treatment choices. The European Network for Health Technology Assessment initiative (EuNetHTA, http://www.eunethta.net) defines HTA as a multidisciplinary process that

summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner, with the aim to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. Economic evaluations are thus an integral part of HTA and reports include a review of previously published economic evaluations for the treatments in questions and may also include a new economic evaluation.

Assessment by HTA agencies support decision-making in healthcare at all levels and are intended for those who make choices regarding healthcare options, including professional caregivers, healthcare administrators, planners and health policy-makers. They can thus be expected to have a strong influence on the uptake of treatments. In some cases there is a direct link between the assessment by the HTA agency and funding for the technology appraised, for example in England/Wales with the National Institute of Clinical Excellence (NICE) or Scotland with the Scottish Medicines Consortium (SMC). In England and Wales there is a direct link between the issuance of a positive guidance on a new drug therapy by NICE and the budget allocated to this new drug therapy by the National Health Service (NHS). Despite of the fact that economic evaluations cannot be transferred from one country to another, guidance documents issued by NICE appear to have an impact on decision-makers beyond the borders of the UK.

There several technology assessment reports of the new biological RA drugs available in Europe, but most are from NICE and concern the two TNF-inhibitors that were first introduced first (etanercept and infliximab). Subsequent updates included the third TNF-inhibitor (adalimumab) as well as early treatment with biologics, and most recently two different molecules (rituximab and abatacept).

- The NHS HTA Programme in England and Wales published a first assessment report in 2002 for etanercept and infliximab that served as basis for the NICE treatment guidelines [6]. This first report assessed the cost per QALY gained with etarnercept or infliximab used at the earliest as a third line DMARD or as a last resort to £70,000-£115,000. This was clearly above the implicit cost-effectiveness threshold of NICE of around £30,000 per QALY gained. However, the subsequent NICE guidance from 2002 [7] did recommend the usage of etanercept and infliximab as a third or subsequent line DMARD based on the HTA.
- An updated assessment report was published in 2006, covering also adalimumab and treatment of early disease [8]. The report concluded that TNF inhibitors are most cost-effective when used as last active therapy, £24,000-38000 per QALY depending on the drug, while first-line use resulted in cost-effectiveness ratios of around £50,000 per QALY. In the updated NICE guidelines from 2007 the recommendation for use of TNF inhibitors remain as third line treatment [9].
- In 2007, NICE published guidelines on rituximab, in the treatment of RA [10]. Rituximab in combination with methotrexate was recommended as second line biologic after failure of at least one tumour necrosis factor α (TNF-α) inhibitor therapy. The decision was based on clinical and cost-effectiveness data submitted by the manufacturer (single therapy assessment).
- The NHS R&D HTA Programme has also evaluated anakinra (interleukin-1 receptor antagonist), and concluded that on the balance of its clinical benefits and cost effectiveness, the drug is not recommended for the treatment of rheumatoid arthritis [11].
- Finally, a guidance for abatacept issued in 2008 (revision planned for 2010) did not recommend its use within the marketing authorization; use was recommended only for patients currently on the drug.[12] The interpretation of this negative guidance is that compared to rituximab, which has the same market authorization (patients failing on TNF-ihibitors) the cost of abatacept is higher, and rituximab is thus preferred as second line treatment after TNF.

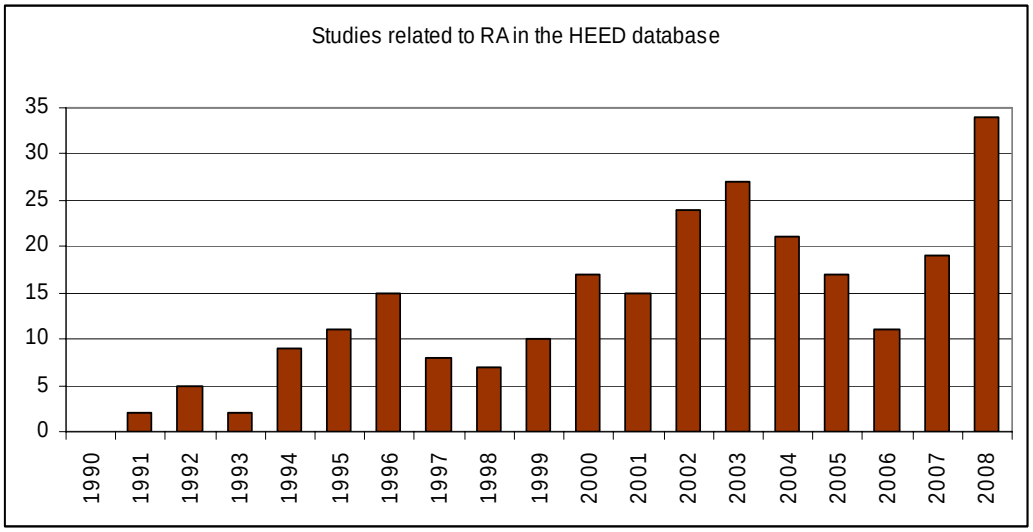
There are few HTA evaluations of biological treatments in RA available from other countries, and these conclude in general that biological treatment (TNF inhibitors) can be recommended for patients who have failed at least two or three standard DMARD therapies, similar to the UK assessments. It is generally acknowledged that the treatments are clinically highly effective, but that their cost-effectiveness is currently less clear.

- The Norwegian HTA agency (The Norwegian Knowledge Centre for the Health Services) published in 2007 an evaluation on TNF inhibitors, in three parts, with the purpose to serve as basis for national guidelines [13]. It included a health technology assessment of adalimumab, etanercept, and infliximab based on a systematic literature review on published economic evaluations. It was concluded that TNF inhibitors do not seem to be cost-effective as first line therapy, no relevant studies are available to evaluate their cost-effectiveness as second line therapy and that in third line TNF inhibitors may be cost-effective, particular for patients with early disease.
- A report by the Danish HTA agency published in 2002 assessed three different scenarios for introduction of TNF inhibitors and likewise concluded that introduction of the drugs in clinical practice was recommended for patients that have failed on other DMARDs [3].
- The Hungarian HTA agency published in 2002 a report on leflunomide but did not include biological treatments.

4.10 Health economic studies in RA

The Health Economic Evaluation Database (HEED) has been developed as a joint initiative between the Office of Health Economics and the International Federation of Pharmaceutical Manufacturers' Associations. It contains information on cost-effectiveness studies and economic evaluations of medicines and other treatments and medical interventions. The database gives an overview of the availability of studies in RA and the figure below presents the number of studies in HEED related to RA published in 1990-2008. In total, 278 RA studies were identified in the database. Not surprisingly, one can observe an increase in published studies around the time of launch of new treatment.

Figure 4-5 Studies on costs, patient outcomes and cost-effectiveness in HEED related to RA between 1990-2008



Economic evaluation in RA has a long tradition. One of the first simple cost-effectiveness analyses was performed using a placebo-controlled 6-month trial comparing auroanofin with placebo as early as 1988.[14] Not surprisingly, in view of the short duration, the study showed no difference between the arms. Two decades later, with the availability of potent disease-modifying treatments, modelling the long term outcome is established and accepted as the standard for cost-effectiveness analyses in chronic diseases such as RA.

As seen in the table above, published studies have shown quite different results, for a number of reasons that are not always immediately obvious. Key differences stem from the general study approach, the underlying data, the assumptions, and to a lesser extent from the analytical methods used. Other obvious reasons are the country of the study, the year of the analysis, the time horizon and, last but not least, the perspective (societal perspective where all costs regardless of who pays are included, or payer perspective where only costs to the particular payer(s) are included). A technical review of early modelling studies performed in the UK highlights how analytical choices may influence the results.[15] Another review of six more recent models provides evidence on more fundamental differences in the general approach to modelling which may or may not lead to different results.[16] Both reviews illustrate also how difficult it is even for specialists to fully understand all details of published models, essentially because of the limited space available for thorough explanations.

Models should represent best available knowledge, and are hence only as good as the underlying data. Regardless of the modelling technique, they should give the same results when using the same data. It is rare, however, that all required data are available, and assumptions regarding a number of parameters are always necessary. Different assumptions will lead to different results. And, by their nature, they can be subject to different opinions, interpretations and critiques.

At introduction of the new biologics, the relevant question was whether they were cost-effective compared to the older treatments, and for which patients. This question is best answered by modelling disease progression with current treatments and estimate changes induced with the new treatment. So far, all of these estimates are based on models. It takes many years and large samples of patients to estimate long-term progression, and a definite cost-effectiveness study for the use of TNF-inhibitors in clinical practice is still elusive. A considerable number of registries have been established in Europe, both specifically for patients treated with biological agents and for those who receive other drugs. However, mean follow-up in most of them is still relatively short. An important question at this point is also whether by combining some of these data sets better information on disease progression on treatment could be gained. Nevertheless, a first cost-analysis of the first year in the Southern Swedish RA registry (SSATG) indicated that all types of costs were reduced for patients treated with TNF-inhibitor, albeit not to the level of the added cost [17]. A first analysis of the British Biologics Registry (BSRBR) using a mean follow-up of 18 month found that treatment with TNF-inhibitors was cost-effective, provided they were used according to the restrictions set forward by the NICE guidance. [18]

Currently, with new market entries, the relevant question is in what sequence these treatments should be used and where in the sequence newly launched drugs should placed. To answer this question data on actual usage of the biologics launched first are required. Although it is still early days, such data are becoming available in the oldest of the registries, mainly in the UK (BSRBR) and in Sweden (ARTIS, and sub registries SSATG and STURE).

Table 4-3 – Published cost-effectiveness analyses

Country	Perspective	Interventions compared	Data source	Patients included (baseline HAQ)	Time-horizon	Result	Currency and year	Ref
Finland	Healthcare provider	infliximab / other standard care		Early disease (1.3)	Mean 21 months	€ 52,000	€ 2007	[19]
Netherlands	Societal	Monotherapy / combination / combination+prednisone /combination+infliximab	Investigator trial	Early disease (1.4)	2 years	infliximab vs. next best alternative: ICER €130,000	€ 2008	[20]
Sweden	Societal	INF+MTX / MTX	Clinical trial	Advanced active RA (HAQ 1.8)	10 years	16,100 €/QALY	€ 2002	[21]
Sweden	Societal	INF and ETA / compared to baseline	Registry	Advanced RA (HAQ 1.5)	1 year	43,400 €/QALY	€ 2003	[17]
Sweden	Societal	ADA+MTX/ DMARD sequence	Clinical trial	Advanced active RA	Lifetime	40-44,000€/QALY	€ 2004	[22]
Sweden	Societal	ETA+MTX / MTX	Clinical trial	Advanced active RA (HAQ 1.8)	10 years	37-46,000€/QALY	€ 2004	[23]
Sweden	societal	Rituximab vs 2nd line TNF	Clinical trial and registry	Advanced RA, TNF failures (1.9)	lifetime	Rituximab dominant	€ 2008	[24]
Sweden	societal	INF /standard care (registry data)	Registry	Advanced RA (1.4)	20 years	19-20,000€	€ 2007	[25]
UK	NHS/PSS	ETA/ DMARD sequence	Clinical trial	Advanced active RA	Lifetime	16,330 £/QALY	GB£ 2005	[26]
UK (NICE)	NHS/PSS	INF/ DMARD sequence; ETA/ DMARD sequence	Clinical trial	Advanced RA	Lifetime	89,970 £/QALY 64,880 £/QALY	GB£ 2004	[27, 28]
UK	NHS/PSS	LEF / SSZ ; LEF / MTX	Clinical trials	Advanced active RA (HAQ 1.3-1.6)	10 years	No difference	GB£ 2002	[29]
UK	NHS/PSS Societal	INF+MTX / MTX	Clinical trial	Advanced active RA (HAQ 1.8)	10 years	34,800 £/QALY 29,900 £/QALY	GB£ 2002	[21]
UK	NHS/PSS	ETA, INF, ADA / DMARD sequence	Registry	Advanced active RA (HAQ 2.1)	Lifetime	23,900 £/QALY	GB£ 2006	[18]
UK	NHS/PSS	RIT 2nd line/standard care	Clinical trial	Advanced RA, TNF-failures (1.9)	lifetime	£11,601 vs biologics £14,690 vs DMARDs	£ 2004	[30]

ADA=adalimumab, ETA=etanercept, INF=infliximab, LEF= leflunomide, MTX=methotrexate, SSZ=sulfasalazine, DMARD=disease modifying arthritic drugs, NHS=National Health Service, PSS=Personal Social Service

4.11 Access to medical care

The guidelines for the use of biologics described above focus on providing the most effective treatments for those patients most in need – patients with severe active and erosive disease - as fast as possible, and to assess their effect rapidly to ensure the best possible treatment. In France, Spain and Sweden it is possible to be prescribed a biologic within 3-4 months; in most other countries the shortest possible time to prescription is 6 months, but mostly lies between 6-12 months.

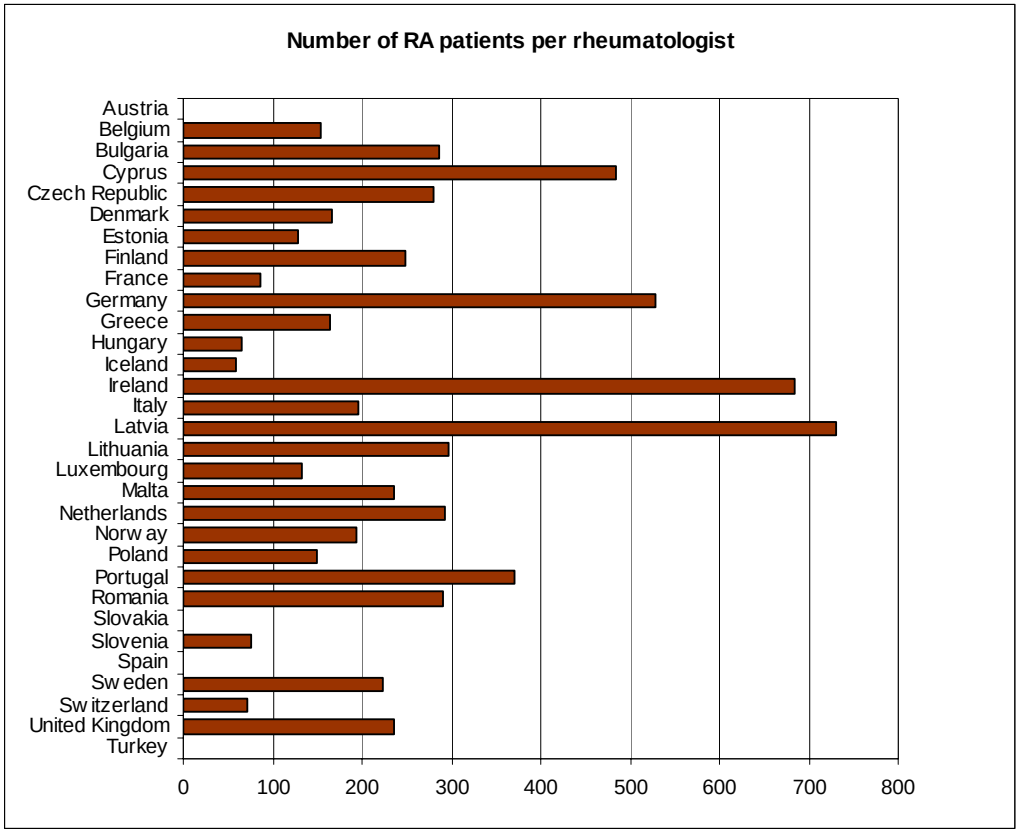
A number of reasons make even the longer delays optimistic in most cases, except for the very severe and very obvious cases. Often, some weeks will go by before a person with RA-like symptoms will seek the help of and be seen by a general practitioner. Some more weeks may pass with NSAID treatment, possibly courses of corticosteroids in severe cases, a number of lab analyses, before referral to a specialist who, in turn, generally has some weeks of waiting time. Even if the specialist then establishes the definite diagnosis within a month or two and starts DMARD treatment, it will take in most cases another 6-12 months before a biologic is actually prescribed. In other words, a delay of 2-3 years until biologic treatment is no exception in many countries. Delays are shorter when there is little doubt about the diagnosis and the disease is severe, but patients with moderate symptoms and difficult to establish diagnosis may wait a long time.

The rheumatology community has made large efforts to promote early diagnosis and early treatment. Reports from the Germany RA registry (Kerndokumentation, Kompetenznetwerk Rheuma, www.rheumanet.org) show that the time to diagnosis and treatment is steadily decreasing; while the mean time from symptoms to a first contact with a rheumatologist was 2 years in 1994, was 1.1 years in 2007 (personal communication, Dr Angela Zink). Surveys by French patient associations in 2003-4 showed delays of 3 years and more, but it appears that this has dramatically changed since then. Also, members in patients associations have often been diagnosed many years earlier, and their answers may give a somewhat biased picture. In 2002, an information campaign for general practitioners was carried out in relation to the start of a large cohort study of early RA patients (ESPOIR). A recent analysis investigated the time to treatment and found that one third of patients had not received a DMARD within 6 months. The main reason for late treatment was diagnostic uncertainty, i.e. the difficulty to reliably assess RA diagnosis as early as the first visits to the rheumatologist. [32, 33]

Treatment within 6 months is thus an organisational challenge even in systems with an easy access to generalists and specialists like France and Spain. In countries where the referral process is slow, e.g. where generalists have a financial interest to treat the patients themselves, or where there is a lack of specialists leading to long waiting times prior to consultation, treatment within 6 months is seldom achieved.

The table below shows the number of patients per rheumatologists, using our prevalence calculations from chapter 1. The data should, however, be handled with great care as the number of rheumatologists officially listed in international or national databases may not be entirely accurate. Not all listed rheumatologists may be actively treating patients; some may be active in research or in the industry. On the other hand, a number of internists and orthopaedists are also treating patients with RA. Finally, in some countries, particularly in the Nordic area and in the United Kingdom, specialist nurses are heavily involved in routine follow-up of RA patients. Nevertheless, the figure gives an indication of the differences among countries in terms of the density of rheumatologists.

Figure 4-6 Number of patients with RA per rheumatologist [source: EUROSTAT]



**The number of rheumatologist is the most recent available. In most countries from 2006 (range 1999-2007). As can be seen in the graph for some of the countries data was not available. The number of RA patients is the previously presented prevalence data.*
Note that numbers of rheumatologists are not available for all countries.

However, from these estimates it does not appear that density of rheumatologists has a systematic influence on the uptake of biologics. Sweden, Norway, Finland and the United Kingdom, with national health care services, have a similar density, yet the Nordic countries have an intensive use of biologics, at the opposite of the United Kingdom. Ireland appears to be one of the countries the least specialists, yet has one of the best uptakes of biologics. Within Western Europe, Germany has the lowest number of specialists and this may indeed partly explain the low usage.

A further complicating factor is that in a number of countries prescription of biologics is not only restricted to specialists only, but beyond that to centres of excellence and with prior authorisation. This appears to be particularly the case in Central and Eastern Europe, but also is an issue in Austria and particularly in Italy, where the number of prescribers has been limited to around 190 for the entire country. This fact, combined with the limitation in hospital drug budget would partly explain the low usage in Italy.

Finally, only two of the established biologics can be self-injected (etanercept and adalimumab), while the third (infliximab), as well as the 3 newer agents launched recently or about to be introduced (rituximab, abatacept, tocilizumab) require infusion. (A further agent that allows self-injection (golimumab) is expected to be

launched shortly.) The number of infused drugs may represent a challenge in some countries, due to the lack of adequate facilities, distance to these facilities and patient preferences. It is however impossible to make a general assessment of this, as it is hospital specific rather than a regional or national issue.

4.12 Conclusion

There is no one explanation for the differences in up-take of the biologics in the different countries in Europe. A number of factors play a role, and their combination is different in each country. The two most important factors are however the macro-economic conditions and treatment guidelines. Overall, we can see that limited usage is a consequence of a low GDP, restrictive treatment guidelines, budget restrictions, administrative hurdles and access to specialists.

4.13 References

1. Douglas K, Bowman SJ. How many patients are eligible for anti-TNF therapy in the UK? Rheumatology (Oxford) 2001;40(12):1416.
2. Symmonds D. Looking back: rheumatoid arthritis--aetiology, occurrence and mortality. Rheumatology 2005;Suppl4(iv14-17).
3. Sundhedsstyrelsen Center for Evaluering og Medicinsk Teknologivurdering. Rheumatoid Arthritis - Health Technology Assessment of diagnosis and treatment Medicinsk Teknologivurdering 2002; 4 (2).
4. PPRI report Pharmaceutical Pricing and Reimbursement Information, European Commission/Austrian Federal Ministry of Health 2008.
5. Emery P, Van Vollenhoven R, Ostergaard M, et al. Guidelines for initiation of anti-tumour necrosis factor therapy in rheumatoid arthritis: similarities and differences across Europe. Ann Rheum Dis 2009;68(4):456-9.
6. Jobanputra P, Barton P, Bryan S, Burls A. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess 2002;6(21):1-110.
7. NICE. Etanercept and infliximab for the treatment of rheumatoid arthritis, NICE technology appraisal guideance No. 36, March 2002. 2002.
8. Chen YF, Jobanputra P, Barton P, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess 2006;10(42):iii-iv, xi-xiii, 1-229.
9. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis, NICE technology appraisal guidance 130, October 2007. 2007.
10. NICE. Rituximab for the treatment of rheumatoid arthritis, National Institute for Clinical Excellence technology appraisal guidance 126, August 2007. 2007.
11. Clark W, Jobanputra P, Barton P, Burls A. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. Health Technol Assess 2004;8(18):iii-iv, ix-x, 1-105.
12. NICE. Abatacept for the treatment of rheumatoid arthritis. April 2008. 2008.
13. TNF- hemmere ved revmatiske Sykdommer 2007 Rapport fra Kunnskapssenteret Nr 12-2006/Nr 2-2007/Nr 16–2007 Kunnskapsoppsummering.
14. Thompson M, Leighton-Read J, Hutchings C, Paterson M, Jr EH. The Cost Effectiveness of Auranofin. Results of a Randomized Clinical Trial. Journal of Rheumatology 1988;15:35-42.
15. Drummond MF, Barbieri M, Wong JB. Analytic choices in economic models of treatments for rheumatoid arthritis: What makes a difference? Med Decis Making 2005;25(5):520-33.

16. Bansback NJ, Regier DA, Ara R, et al. An overview of economic evaluations for drugs used in rheumatoid arthritis: focus on tumour necrosis factor-alpha antagonists. Drugs 2005;65(4):473-96.
17. Kobelt G, Eberhardt K, Geborek P. TNF-inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow-up study of patients with RA treated with etanercept or infliximab in southern Sweden. Ann Rheum Dis 2004;63:4-10.
18. Brennan A, Bansback N, Nixon R, et al. Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology (Oxford) 2007;46(8):1345-54.
19. Virkki LM, Konttinen YT, Peltomaa R, et al. Cost-effectiveness of infliximab in the treatment of rheumatoid arthritis in clinical practice. Clin Exp Rheumatol 2008;26(6):1059-66.
20. Vanden Hout W, Goekoop-Reuterman Y, Allaart C, al e. Cost-utility analysis of treatment strategies in patients with recent onset rheumatoid arthritis. Arthritis Rheum 2009;61(3):291-9.
21. Kobelt G, Jönsson L, Young A, Eberhardt K. The cost-effectiveness of infliximab (Remicade(R)) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. Rheumatology 2003;42(2):326-35.
22. Bansback NJ, Brennan A, Ghatnekar O. Cost effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden. Ann Rheum Dis 2005;64(7):995-1002.
23. Kobelt G, Lindgren P, Singh A, Klareskog L. Cost effectiveness of etanercept (Enbrel) in combination with methotrexate in the treatment of active rheumatoid arthritis based on the TEMPO trial. Ann Rheum Dis 2005;64(8):1174-9.
24. Lindgren P, Geborek P, Kobelt G. Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden. Int J Technol Assess Health Care 2009;25(2):181-9.
25. Lekander I. ISPOR abstract 2008.
26. Brennan A, Bansback N, Reynolds A, Conway P. Modeling the cost-effectiveness of etanercept in adults with rheumatoid arthritis inthe UK. Rheumatology 2004;43:62-72.
27. Jobanputra P, Barton P, Bryan S, Fry-Smith A, Burls A. The clinical effectiveness and cost-effectiveness of new drug treatments for rheumatoid arthritis: etanercept and infliximab. Birmingham: University of Birmingham; 2004.
28. Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with chronic conditions: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technology Assessment 2004;8:1-91.
29. Kobelt G, Lindgren P, Young A, Eberhardt K. Cost and Effects of Leflunomide in the UK. Eur J Health Econom 2002;3:173-9.
30. Kielhorn A, Porter D, Diamantopoulos A, Lewis G. UK cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. Curr Med Res Opin 2008;24(9):2639-50.
31. Brennan A, Bansback N, Nixon R, et al. Modelling the cost effectiveness of TNF-{alpha} antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology (Oxford) 2007.
32. Benhamou M, Rincheval N, Roy C, et al. The gap between practice and guidelines in the choice of first-line disease modifying antirheumatic drug in early rheumatoid arthritis: results from the ESPOIR cohort. J Rheumatol 2009;36(5):934-42.
33. Lukas C, Guillemin F, Landewe R, et al. Factors determining a DMARD initiation in early inflammatory arthritis patients. The ESPOIR cohort study. Clin Exp Rheumatol 2009;27(1):84-91.

Chapter 5 - The Value of Treatment in RA

We gratefully acknowledge the contribution of Ronald van Vollenhoven, MD and Jenny Augustsson (Karolinska Institute, Stockholm, Sweden) for access to pre-published data.

CONTENT

5 The Value of Treatment in RA....5:2
5.1 Summary....5:2
5.2 Introduction....5:3
5.3 Cost-effectiveness in clinical practice....5:4
5.4 Results that affect cost-effectiveness....5:5
5.4.1 Effects on quality of life and utility....5:5
5.4.1.1 RA population....5:5
5.4.1.2 Utility in patients treated with biologics....5:7
5.4.2 Effects on costs....5:9
5.4.2.1 Direct cost-savings....5:11
5.4.2.2 Indirect cost savings....5:12
5.5 Conclusions....5:16
5.6 References....5:16

TABLES

Table 5-1 – Risk factors for indirect costs [17]....5:14
Table 5-2 Ten-year cost and QALY differences by HAQ at treatment start [18]....5:15

FIGURES

Figure 5-1 Correlation between QoL (utility) and functional capacity (HAQ) [5, 6]...5:5
Figure 5-2 Change in health status over time (SF-36) [7]....5:6
Figure 5-3 Change in function and utility over time (HAQ, EQ-5D) [7]....5:6
Figure 5-4 – Utility change with TNF-inhibitor treatment in clinical practice[10]....5:7
Figure 5-5 Utility change after 21 months treatment [12]....5:8
Figure 5-6 – Relationship of Costs to HAQ [6]....5:10
Figure 5-7 – Changing structure of costs with advancing disease [5]....5:10
Figure 5-8 Reductions in costs in the first year of TNF-inhibitor treatment [3]....5:11
Figure 5-9 Decrease in outpatient consultations with anti-TNF therapy [12]....5:12
Figure 5-10 Weekly working hours lost by baseline HAQ [12]....5:13

5 The Value of Treatment in RA

5.1 Summary

This chapter discusses current knowledge of the value of biologics, focusing on parameters that affect health economic results. However, a comprehensive review is beyond the scope of this chapter. Rather, issues are illustrated with pertinent examples.

Over the past decade we have witnessed important advances in the management of RA, with development of novel tools for outcome assessment, innovative therapies and new intensive and dynamic therapeutic strategies. As a consequence, disease remission is today a realistic goal for many patients, if available treatments are used to their full potential.

The new biologic treatments have been shown to be extremely effective in not only reducing signs and symptoms of the disease, but also halt or slow the underlying joint destruction, and even improve cardiovascular events/mortality. They come at a substantial immediate cost concentrated on those payers responsible for the drug budgets, while potential savings are long term and occur with some degree of uncertainty to many other stakeholders. Usage of biologics has thus initially been restricted to those patients in greatest need where they are considered to be cost-effective based on early models.

Despite a decade of their use, it is still too early to evaluate the full impact of these treatments in clinical practice. In the short term, some health care costs can be off-set, but the majority of the impact lies in the future, if progression to severe disability can be avoided or at least reduced.

However, a wealth of data on individual clinical and/or economic parameters that affect the cost-effectiveness of these treatments is emerging. They all point towards large improvements in quality of life, function and disease activity, as well as savings and cost-offsets..

5.2 Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory joint disease that can affect virtually all joints, but most commonly involves hands and feet, followed in frequency by the wrist, knee and other large joints of the extremities. Onset can be insidious or acute, but in the majority of patients the course is progressive leading to destruction of joints, functional disability and reduced quality of life. RA is associated with increased morbidity and mortality, mostly due to the cardiovascular consequences of chronic inflammation, and an increased frequency of lymphomas in relation to the severity of the disease [1].

Over the past decade we have witnessed important advances in the management of RA, with development of novel tools for outcome assessment, innovative therapies and new intensive and dynamic therapeutic strategies. As a consequence, remission can be observed in one of five patients [2], and even better success can be expected with the addition of further treatments.

The main goal of RA therapy to modify of the disease and slow progression is thus within reach for many patients, if available treatments are used to their full potential.

Traditionally, management of RA involves both medicinal and non-medicinal strategies. Non-medicinal strategies include on the one hand psychological counselling, physiotherapy and occupational therapy, and on the other hand orthopaedic surgery with joint conservation or joint replacement. Medicinal strategies include symptomatic agents such as non-steroidal anti-inflammatory drugs (NSAIDs) or analgesic agents, glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs).

Whereas symptomatic agents reduce the signs and symptoms of RA, they fail to interfere with the processes leading to joint damage. In contrast, DMARDs can not only effectively control signs and symptoms, but also slow join erosions, and have been used earlier and earlier in the disease process. Traditional small molecules are gold salts, antimalarials, salazopyrine, methotrexate and leflunomide, and among these, methotrexate is regarded as the most effective and currently standard initial therapy particularly in active disease. However, many patients will not experience even a 50% improvement of signs and symptoms with these treatments, despite frequent switching, dose increases and combination treatment.

For these patients, biologic treatments provide the only effective treatment option. The first successful compounds, 3 TNF inhibitors (etanercept, infliximab, adalimumab), have shown convincingly in a number of studies to lead to rapid clinical improvement, reduction in physical impairment and significant retardation or even half of joint damage both in established and early RA, particularly in combination with methotrexate. The more recent agents, with different mechanisms of action (rituximab, abatacept, toculizumab) have in turn shown to be effective in patients with an inadequate response or intolerance to a TNF-inhibitor. (For a summary on clinical effects, see Smolen and Aletaha [1].)

5.3 Cost-effectiveness in clinical practice

Despite of this uncontested clinical effect, the use of biologic agents is restricted in many ways, due to their price. Partly this may be due to budgetary or affordability reasons, partly due to the fact that the value (what one obtain) is perceived not to be in line with the price (what one pays). However, the evidence of the value is continuously built up with new trials, but most of all with data from clinical practice and registries. It is, however, still not possible to perform a full cost-effectiveness analysis based on actual use in clinical practice, essentially because the largest benefit – the absence or reduction of permanent functional disability associated with lower costs and higher quality of life – lies in the future. Thus, even with close to 10 year follow-up data in the longest-standing registries, modelling is still required.

For cost-effectiveness analysis, registries present a number of challenges. The biggest issue to tackle when using registry data is the comparator group. This is particularly difficult when using the early years in the registries, as in most countries all those very severely ill patients who qualified initially for anti-TNF drugs were indeed treated, as shown in an early Swedish study [3]. Patients of a similar severity level on standard treatment were likely those who either could not tolerate the biological treatments or could not take them for other reasons. The study thus analysed the change compared to baseline and is thus not a full cost-effectiveness analysis. In contrast to the Swedish analysis, the recent study in the UK was based on 7083 patients treated with anti-TNF drugs and 870 controls treated with standard DMARDS from the same registry [4]. Both groups had active disease and substantial functional disability at baseline. However, mean disease duration was 9.9 years in the control group versus 14.1 years in the anti-TNF group, and mean HAQ scores were 1.6 in the control group versus 2.1 in the anti-TNF group. Although modelling techniques allow adjusting for such a difference, the question remains whether these 870 patients are truly comparable or whether they represent a group that either does not qualify, cannot tolerate, or has withdrawn from anti-TNF drugs. Nevertheless, as the group on biologics had more severe disease, the findings likely under- rather than over-estimate the cost-effectiveness.

Considering these difficulties to perform a “real-life” cost-effectiveness analysis, we present in this chapter a number of findings from clinical practice with particular relevance to the burden and the cost of RA. (Modelling studies based on clinical trials are not included here but will be presented in the last chapter.) These represent illustrations rather than an exhaustive overview that would be beyond the purpose of this chapter. Findings presented include

- the effect on quality of life (QoL) and utility
- the effect on mortality
- the long term cost depending on when treatment is started
- the effect on direct costs
- the effect on indirect costs
- the effect of management

as well as a short discussion on drug dosing and cycling, management strategies and adverse events.

Within this discussion, we take the clinical effect on inflammation, disease activity and erosions as a given.

5.4 Results that affect cost-effectiveness

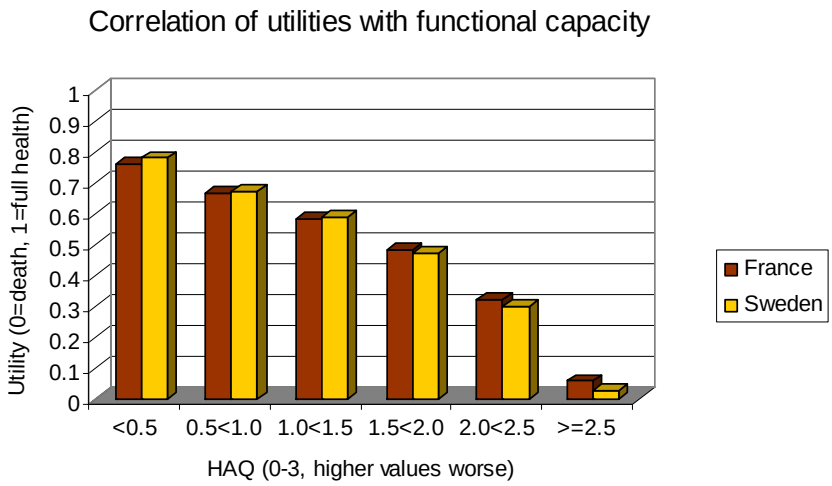
5.4.1 Effects on quality of life and utility

5.4.1.1 RA population

In RA, health related QoL is an important outcome measure both from the clinical and the health economic point of view. One has no difficulty to accept that, in general, patients with a better QoL will consume fewer health care resources.

The widely used Health Assessment Questionnaire (HAQ) is not a QoL instrument, but measures patient-reported functional capacity. However, its correlation with QoL has been shown in numerous studies, using instruments such as the Short Form 36 (SF-36) or the EQ-5D (utility): A decrease in HAQ will correspond to an increase in QoL and utility, as illustrated below.

Figure 5-1 Correlation between QoL (utility) and functional capacity (HAQ) [5, 6]



The SF-36 can show the improvements in different individual aspects of health related quality of life. The instrument is widely used in all indications and thus allows comparison across diseases. When used repeatedly, it allows investigating the development of QoL over time. This was investigated in the Norwegian RA registry, and results showed that between 1994 and 2004, overall health status of patients with RA improved [7]. The number of respondents between 20 and 79 years of age were 931, 1025, 829 and 914 in 1994, 1996, 2001 and 2004, respectively. SF-36 scores, both the individual domains and the physical and mental summary scores increased (improved) over the 10 years. At the same time, mean HAQ decreased from 1.68 to 1.55, utility increased from 0.616 to 0.647, and for both the change was more noticeable in 2001 and 2004. It is not possible to link these results directly to the introduction of the biologic drugs, but it is noteworthy that in 2001 3.1% of patients and in 2004 11.8% of patients were on biologic treatment.

Figure 5-2 Change in health status over time (SF-36) [7]

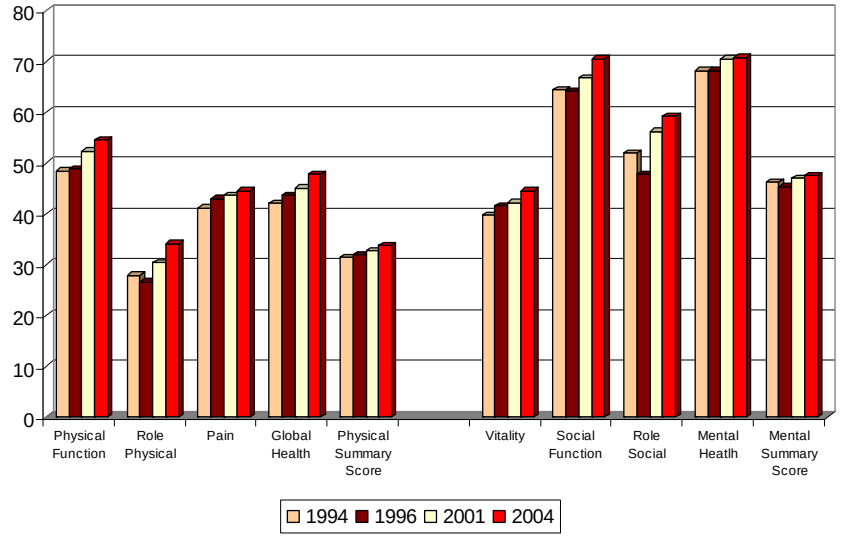
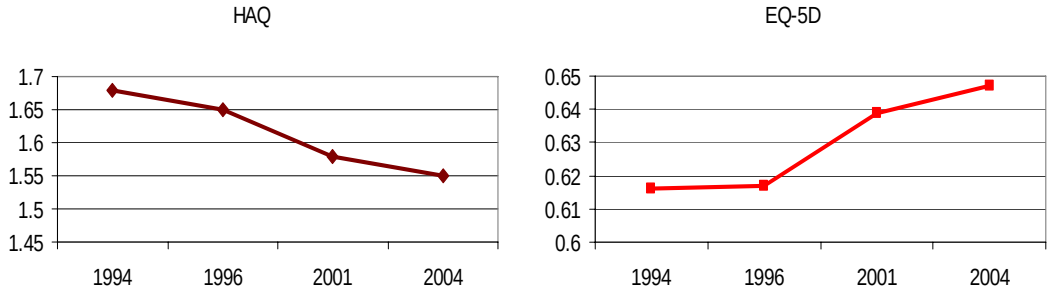


Figure 5-3 Change in function and utility over time (HAQ, EQ-5D) [7]

Function **Utility**



The authors speculate that the results are a consequence of wider access to better and more aggressive treatments. Indeed, since the early 90's, RA treatment has evolved and the most effective DMARDs, including biologics, are introduced early in the disease course.

An analysis of the effect of prescription practice of TNF-inhibitors on treatment response in the Danish nationwide biologics registry (DANBIO) showed that practice has indeed changed towards patients with lower disease activity [8]. Baseline disease activity for 1813 patients recorded in the registry between 2000 and 2005 decreased from 5.9 to 5.3 (DAS28). Despite of this, treatment response increased significantly from 1.8 to 2.2 units (DAS28), good response rates as defined by the European League against Rheumatism (EULAR) from 28% to 50%, 50% improvement rates as defined by the American College of Rheumatology (ACR) from 31% to 51%, while no response decreased from 29% to 16%. Drug survival was around 70% in all years.

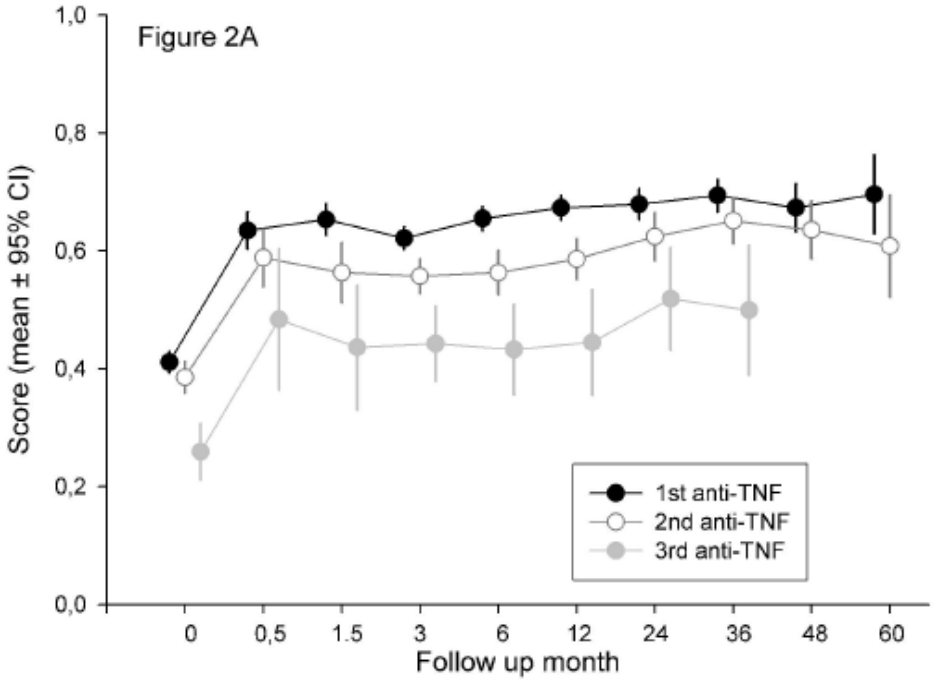
Thus, not only does overall better access and management improve patients' health status, more intensive management and earlier treatment with biologics also provides better response. This should logically lead to savings in costs other than the intervention costs. This has also been shown in a Scottish study (TICORA) where patients were randomized to intensive and standard management (see under "Effects on costs" [9].

5.4.1.2 Utility in patients treated with biologics

5.4.1.2.1 Treatment Effect

In the Southern Swedish biologics registry (SSATG), the registry with probably the longest follow-up of patients treated with biologics, the EQ-5D is used routinely to measure patients' health status. The rapid and sustained utility gain with TNF-inhibitor treatment has been documented over time as well as for different lines of treatment, i.e. patients who switch to a second or third TNF-inhibitor due to either adverse events or lack of effect [10]. The analysis included 2554 patients with RA and showed a utility gain of around 0.25 already after 2 weeks' treatment, and maintained thereafter for 5 years if treatment continued. In an earlier analysis of the first 116 patients included in SSATG, the initial utility increase was shown to be significantly correlated with an increase in HAQ [3].

Figure 5-4 – Utility change with TNF-inhibitor treatment in clinical practice[10]



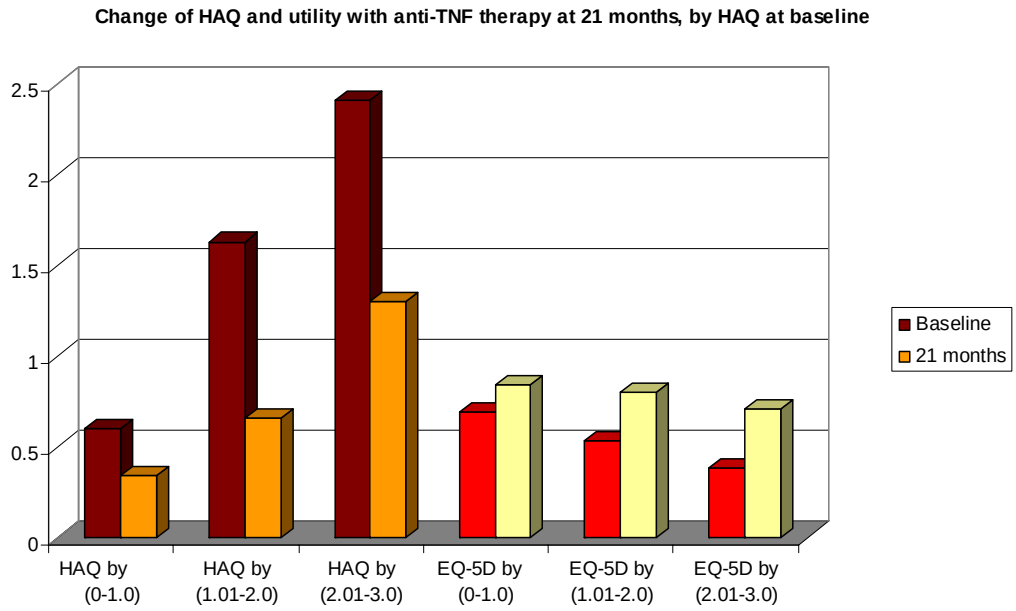
Reproduced with permission, Ann Rheum Dis 2009

The change shown above for the large sample of patients in SSATG is lower that what was seen in the first 116 patients included in the registry. Compared to the full sample, these patients had considerably lower baseline utilities (0.28 versus 0.4). Although the full analysis found no significant temporal trend, i.e. the change was similar despite a slight increase in baseline utility over time [10], the low baseline of this early severe sample may explain the larger gain [3].

In both analyses, patients reached a utility of around 0.65, and one could speculate that this represents a type of a "ceiling level" for patients who have had the disease for years of the disease. Indeed, joint damage is irreversible and thus limits the magnitude of the effect on utility that can be achieved with treatment. In view of the correlation of utility with HAQ, this can be implied directly from the findings of an irreversible part of HAQ in established disease [11].

A recent analysis of 740 patients enrolled in the Alberta Biologics registry and treated with TNF-inhibitors showed a similar utility improvement [12]. The authors investigated responses by baseline severity of HAQ. For patients with a HAQ between 0 and 1, utility improved by 0.15 to basically normal population values; patients between HAQ 1 and 2 improved by 0.27; patients between HAQ 2 and 3 improved by 0.33. Utility improvement was parallel to an improvement in HAQ of 0.26, 0.97 and 1.11, respectively. All changes were significant ($p<0.001$).

Figure 5-5 Utility change after 21 months treatment [12]



Reproduced from [12]

In the Swedish analysis above, first and second line treatment showed similar results at the group level in this analysis. However, a responder analysis in the same sample using ACR and EULAR criteria showed that response was lower for second time switchers. Response rates to the second and third TNF-inhibitor at the group level were ACR50 27% and 18%, EULAR good response 25% and 9% respectively. [13] Another analysis from the Stockholm Biologics Registry (STURE) showed that response to the second or third TNF-inhibitor may be dependent on the reason for discontinuing the first: lack of effect or adverse events. [14] Patients with insufficient response to a first TNF-inhibitor had an improved response with a second TNF-inhibitor; patients discontinuing due to adverse effects but with a certain level of response on the first treatment achieved at least a similar response on the second similar treatment.

Currently, physicians have more treatment options with different classes of drugs at their disposal, allowing more individualized treatment and improved outcome. On could thus speculate that once patients have been initiated on biologic treatment, the utility gain is maintained as long as they remain on treatment with any of the available biologics.

5.4.1.2.2 The value of utility increases

An increase in utility can be transformed into quality-adjusted life-years (QALYs). The QALY is the outcome measure of choice of European authorities who formally use economic evaluation in reimbursement or funding decisions. QALYs are a combination of years of life and quality of life, where years are weighted with their utility. Although no formal threshold exists as to how much society is willing to pay for a QALY gained, an unofficial limit of around €50,000 is often assumed.

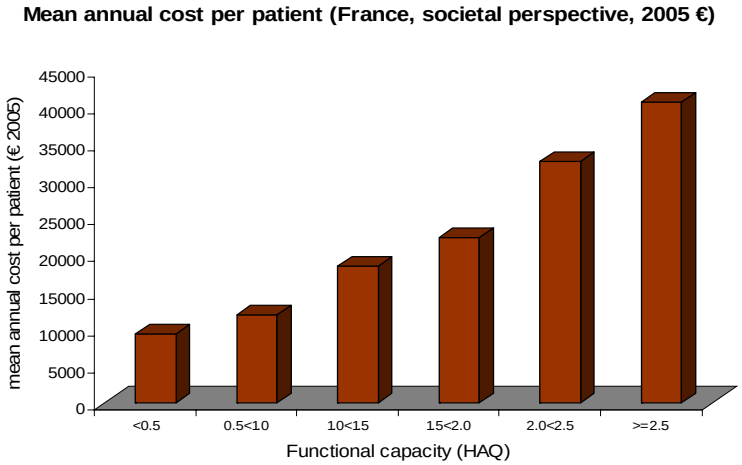
The value of an increase in utility by 0.20-0.25 and the maintenance at this level thus yields 0.20-0.25 QALYs every year for patients on treatment. Using the above unofficial threshold, the value of this improvement can then be estimated at around € 10-12,500 per year.

This calculation requires discussion. The implied value is close to or slightly less of the annual cost of the biologics, depending on the country, and one could be tempted to argue that this shows their cost-effectiveness. However, it is calculated using only patients who remain on treatment, and it is necessary to use an intent-to-treat approach, where treatment costs for patients that start treatment and discontinue, as well as the cost of monitoring and treating adverse events is incorporated. Thus the annual treatment cost increases above the value of the health gain, and it is crucial to manage treatment in a way that avoids wastage as much as possible. On the other hand, with improved health status come generally reductions in the use of resources, both health care and other resources, leading to cost-offset.

5.4.2 Effects on costs

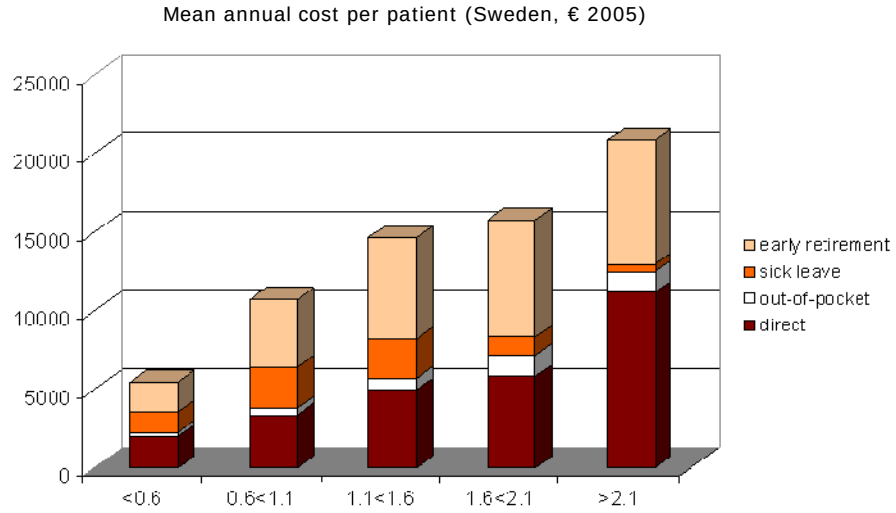
A number of studies have shown the correlation between HAQ and all type of costs. The largest and most recent comprehensive study from France illustrates this relationship.[6]

Figure 5-6 – Relationship of Costs to HAQ [6]



A similar study in Sweden investigated drivers of different types of costs. [5] The analysis showed that HAQ was by far the strongest driver of all types of costs, with the exception of short-term sick-leave where disease activity was found to be a stronger predictor. This is not surprising, as sick-leave is mostly a cost earlier in the disease, as shown below, when patients are still in the workforce; later in the disease, a majority of patients will have stopped working. It is hence inflammation and related pain and fatigue, rather than irreversible functional disability that will drive the need for short term absences.

Figure 5-7 – Changing structure of costs with advancing disease [5]



The change in HAQ scores observed in clinical trials are often around 0.5, and even in the sample of patients with long-standing disease in SSATG HAQ changed by 0.4. Within the framework shown above, this would imply for most patients a move to a better HAQ category, and hence theoretically cost off-sets. If we were to perform the same simplistic calculation as we did for utilities above, a patient who improved from HAQ 1.5 to 1.0 will have a cost-reduction of around € 4.000 in Sweden and around € 6.000 in France.

Again, this requires discussion. Such cost off-sets in the short term can only be realised in direct costs (health care costs, out-of-pocket costs and informal care) and short term sick-leave. Reduction in production losses due to early retirement or mortality, where the potential gain is much larger, will only materialize in the long term. Patient on invalidity pensions may not be able to return to work for reasons other than their disease; savings will thus come from avoiding that patients have to leave the workforce. The mortality risk results from continuing severe inflammation; reduced mortality will hence only be observed after some years.

After 10 years of usage of biologics in RA, data on all of these savings are emerging, and we illustrate some of the studies below.

5.4.2.1 Direct cost-savings

One of the first studies that investigated changes in costs with biologic treatment was the 1st year analysis of the Southern Swedish Biologics Registry (SSATG) [3]. Within this first sample of 116 patients with severe and long-standing disease (mean disease duration 14 years, DAS28 5.9), all direct resource consumption with the exception of outpatient consultations decreased during the first year of treatment compared to the previous year. In particular, hospitalisation and surgery costs decreased substantially. Consultations would be expected to increase initially as treatments such as the biologics would be more closely monitored than small molecule DMARDs, particularly in the beginning.

Figure 5-8 Reductions in costs in the first year of TNF-inhibitor treatment [3]

Table 2 Mean costs per year (€, 2002) and utilities

	Baseline Mean (SD)	12 Months Mean (SD)	24 Months Mean (SD)
Utility	0.28 (0.33)	0.65 (0.23)	N/A
Work capacity, full sample (%)*	27	28	N/A
Work capacity, patients <65 (%)	31	33	N/A
Sick leave (days)	1.6 (5.0)	1.1 (2.6)	N/A
Indirect cost*	21880 (17030)	21739 (18110)	N/A
Total cost cortisone	97 (95)†	44 (52)	34 (44)
Total cost NSAID	117 (81)†	89 (87)	87 (87)
Total cost analgesics	63 (51)†	51 (49)	54 (50)
Total cost DMARD	289 (734)†	109 (387)	98 (343)
Total cost hospital	3823 (7179)‡	1963 (3839)	N/A
Total cost surgery	569 (989)‡	356 (675)	N/A
Outpatient visits§	367	568¶	N/A
Acute care visits§	246	143	
Total cost anti-TNF treatment		14704 (3065)**	16202 (3584)
Total costs	27447 (20933)	39630 (20829)	N/A

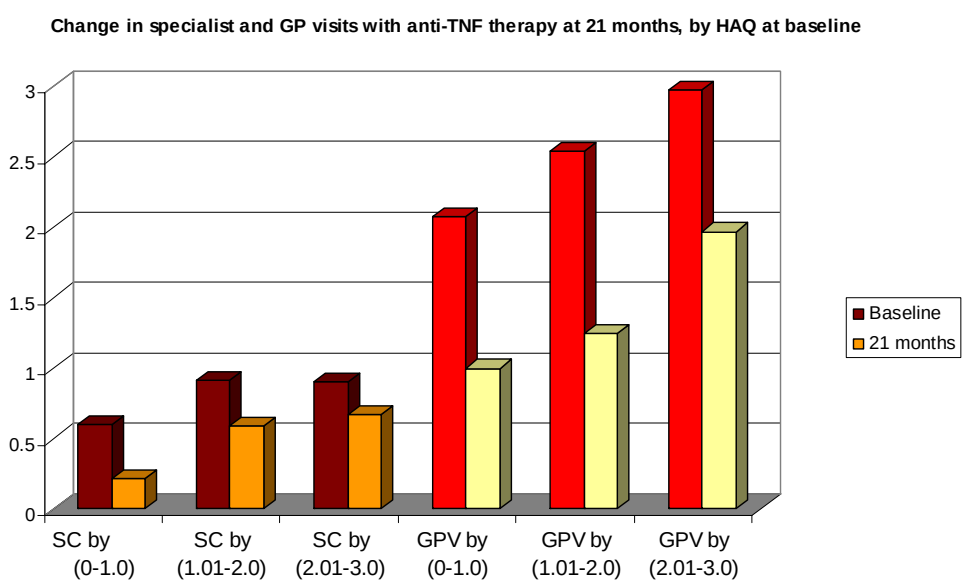
1 €=9.05 SEK.
*Baseline and 12 months' status for the entire cohort, extrapolated to annual costs. Work capacity is expressed as full time equivalent—that is, full time work represents 100%, part time work actual percentage, and not working 0%; †usage at baseline, extrapolated to costs for the previous year; ‡retrospective data, previous year; §mean number of visits of the Lund cohort; ¶including visits for administration of infliximab; **use during study year.

Reproduced with permission, Ann Rheum Dis 2004;63:4-10

Similar findings were shown in a study designed to retrospectively assess drug utilisation and dosing patterns of TNF-inhibitor therapy in 44 centres across Europe (DART study) [15]. The study included 739 patients with a mean disease duration of 15 years. Compared to the year prior, inpatient consumption decreased overall (by 47% and 38% for etanercept and adalimumab, respectively, but increased due to infusions for infliximab). Joint surgery decreased between 40%-67%, diagnostic procedures decreased by 32%-43%, but outpatient consultations and laboratory analysis increased, partly due to the study protocol where at least 3 visits were required.

The registry analysis from Alberta (Canada) on the other hand showed a clear and significant reduction in consultations over 21 months, compared to pre-therapy [12]. The decrease was inversely related to the severity of functional handicap at baseline.

Figure 5-9 Decrease in outpatient consultations with anti-TNF therapy [12]



SC = specialist (rheumatologist) consultation
GPV = general practitioner visit
Reproduced from [12]

5.4.2.2 Indirect cost savings

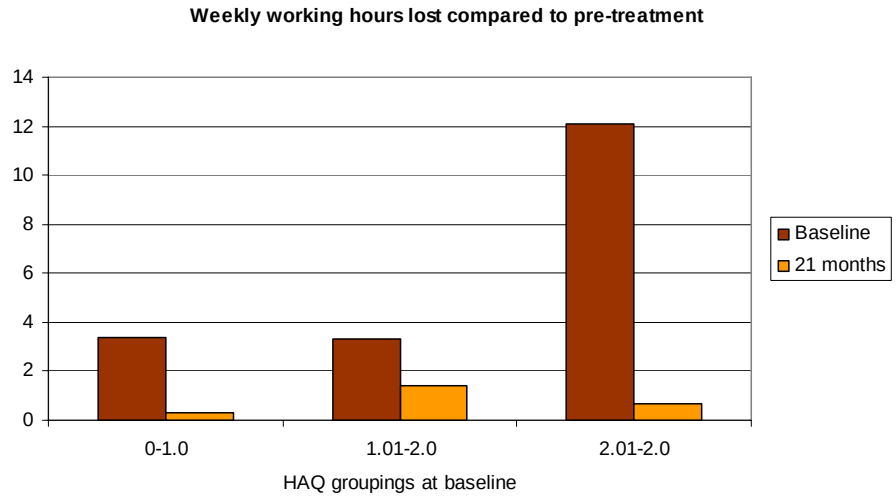
Indirect costs are resources lost due to a disease, such as the loss of work capacity. We distinguish short term losses (sick leave), and long term losses (loss of work capacity due to disease and premature mortality). They are costs to society rather than the health care system in terms of lost production, and are most often valued using the gender and age specific cost of labour in a given country. When estimating costs to public payers, they are valued using the per diem sick-leave compensation and invalidity pensions.

Production losses represent the largest potential for cost reductions in RA, but take the longest time to materialize and thus are the most difficult to show. Even 10 years after the introduction of biologic treatments it is too early to measure their full impact on production losses. However, it is probably currently the most intensely research area, and all data point towards improvements in work capacity and thus reductions in societal costs. A number of clinical trials have evidenced significant differences in work absences between patients treated with biologics, generally in combination with methotrexate, and methotrexate alone (e.g. the TEMPO and COMET trials with etanercept, the PREMIER trial with adalimumab).

In clinical practice, data are also emerging. Even during the early year of treatment in the Southern Swedish biologics registry (SSATG), two patients returned to work and mean sick-leave was reduced by half a day from 1.6 to 1.1 days (see above).

The analysis from the Alberta registry in Canada show a striking in the reduction of weekly working hours lost, with basically hardly any absence regardless of baseline HAQ during 21 months compared to pre-treatment. Although this study is not from Europe but Canada, there is no reason to believe that these results should not apply to Europe as well – with obviously different cost consequences.

Figure 5-10 Weekly working hours lost by baseline HAQ [12]



Reproduced from [12]

A similar analysis was performed for the Stockholm biologics registry (STURE) and showed very similar results [16]. Significant improvements in hours worked per week were observed already at 6 months (+2.4h), with further increases compared to baseline at one year (+4.0h) and two years (+5.3h). Using regression analysis, an increase in time worked of 4.2 hours per week during the first year and 0.5 hours in subsequent years was estimated. This corresponds to an decrease in production losses of around 12% per year (based on average actual working time weighted by gender of 36 hours in Sweden) and a reduction in production losses of around €3500-4000 per year.

A French study investigated the determinants of indirect costs in a mail survey performed with a patient association [17]. Mean age of respondents (N=1189) was 53 years, with a mean disease duration of 15 years, and half of the sample was employed at the time of the survey. For these, short term absences averaged at 11.6 days during the previous 6 months. Slightly over one third of patients (34.5%) were on early retirement and received invalidity pensions as a consequence of RA. Average annual indirect costs from the perspective of the French public payers were estimated at €3,210 per patient. In a model, the authors first estimated the probability of having indirect costs, and then the probability of having costs exceeding € 4,000. The strongest influence on production costs were found for HAQ, treatment with a biologic, and failure of at least one biologic treatment. Higher education predicted both a lower risk for indirect costs and lower costs. Patients on small molecule DMARDs at twice the risk of having indirect costs compared to patients on biologic treatment, and four times the risk of exceeding €4,000. Similar results were found for patients who had failed at least one biologic treatment.

Table 5-1 – Risk factors for indirect costs [17]

Parameters	*Odds Ratio for having indirect costs*	*Odds ration for having indirect costs exceeding €4,000/year*
Age ≥ 55 vs < 55	0.382 *	2.086 **
High vs low education	0.464 *	0.571 **
HAQ severe vs mild	3.804 *	3.831 **
HAQ moderate vs mild	2.302 *	1.771 **
Comorbities 1-2 vs 0	1.813 **	1.648
DMARD vs biologic	**1.938**	**4.808 ***
Failure on at least 1 biologic	**2.811 ***	**4.009 ****

* significant at the 1% level; ** significant at the 5% level
Reproduced from [17]

In cross-sectional samples, short term indirect costs represent around 25% of total production losses [6, 17]. The largest decrease in indirect cost will thus come from a reduction in early retirement due to the disease. As discussed above, this has so far not been shown in clinical practice due to the short time since the use of biologic drugs. Some studies have investigated the risks of loosing work capacity in the future. However, such studies are inherently difficult and require large samples over a number of years. Work capacity is influenced by a number of other factors than disease. A decline in overall economic activity will influence the attribution of invalidity pensions as well as the return to work of patients. Co-morbidities will also have an impact, and particularly in RA it is not always easy to separate between patients with RA and hence a number of related co-morbidities and patients with RA and unrelated other diseases. Thus, the best way to investigate early retirement is most likely a trend analysis in a national data base that can be linked to a number of parameters such as biologic treatment, other diagnoses and general rates of attribution of invalidity pensions.

However, a number of factors make it reasonable to expect that indirect costs will decrease in the long term:

- there is a clearly demonstrated link between decreasing functional capacity and reduced ability to work
- a reduction of short term sick leave was demonstrated in several studies
- biologic treatment leads to impressive improvements in HAQ that are both rapid and maintained when remaining on biologic treatment.

Reductions in early retirement require, however, that patients are treated early, when irreversible joint damage and related disability is absent or minimal.

The effect of early versus late treatment was investigated in a modelling study based on 9-year follow-up data in the Southern Swedish biologics registry (SSATG).[18] A total of 1903 patients starting TNF-inhibitor treatment were available, with 633 patients switching to a 2nd and 170 patients to a 3rd biologic. Using patient level data, the model represents treatment as observed (including switching and discontinuation) and estimates total treatment costs and QALYs.

When treatment is started late (at HAQ 1.85), discounted costs are almost 20% higher over 10 years then when starting at HAQ 1.33 as the sample in the registry. More importantly though, patients initiating treatment at HAQ 1.85 lost one full QALY compared to those starting at HAQ 1.33. These results are, however, still based on patients with relatively long-standing disease, with many patients having left the workforce. This reduces the potential for maintaining work capacity, and one could speculate that in patients with early disease, results would be even more telling.

Table 5-2 Ten-year cost and QALY differences by HAQ at treatment start [18]

	Total cost per patient starting biologic treatment 10 year horizon (discounting 3%)		
	Start HAQ 1.33	Start HAQ 0.85	Start HAQ 1.85
Direct cost	€ 99,000	€ 91,000	€ 118,000
Indirect cost	€ 91,000	€ 82,000	€ 109,000
Total cost	€ 190,000	€ 173,000	€ 227,000
QALYs	4.4	5.3	3.4

5.4.2.2.1 Productivity at work

An additional production loss that might be important to consider in a disease with symptoms such as pain and fatigue is reduced productivity while at work. This type of production loss is very difficult to quantify, as the only possibility is to ask the patient to judge how "normal" his work output has been in the past few days. A number of instruments exist, among them the WPAI (work productivity and activity index) by Reilly and colleagues, but they all have to rely on this type of direct question. While it is thus possible to measure the impact of advancing disease on productivity at work by comparing the impact among patients with different disease severity or functional disability, it is preferable to use a control group when investigating the overall reduction of productivity at work due to RA.

Within the field of RA, reduced productivity at work has indeed been measured in some clinical trials (e.g. PREMIER [19]). Findings suggest that in patients under biologic treatment the effect of the disease on work activity was significantly reduced, compared to treatment with methotrexate alone.

5.4.2.2.2 Mortality

In patients with severe active RA such as those qualifying for biologic treatment, mortality is increased, in part due to cardiovascular disease [20]. A Canadian meta-analysis estimated that the cardiovascular risk is increased by 50% in patients with RA [21]. A model based on the ARAMIS data base in the United States estimated that, compared to normal life expectancy of 22 years, patients with RA followed in ARAMIS had a life-expectancy of 18.6 years [22]. Evidence is emerging that the cardiovascular risk is reduced in patients treated with TNF-inhibitors [23]. Although many of these patients may be older than normal retirement age, a proportion will be younger and could be assumed to remain in the work force. However, no studies so fare exist.

5.5 Conclusions

The impact of treatment with biologics on cost is both short term and long term. In the short term, direct costs will increase due to the cost of the treatments, but some parts of it are off-set even in the short term by savings in other health care costs such as hospital admissions, surgical interventions, etc. Further cost off-sets will occur in the long term to society, as patients remain in the workforce longer.

It is still too early to evaluate the full effect, but a large number of individual findings and studies point towards reductions in all types of costs with biologic treatment, provided they are use for the right patients, at and for the right time and in the right way.

5.6 References

1. Smolen J, Aletaha D. The burden of rheumatoid arthritis and access to treatment: a medical overview. Eur J Health Econ 2008;8 Suppl 2:S39-47.
2. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. Rheumatology (Oxford) 2007;46(6):975-9.
3. Kobelt G, Eberhardt K, Geborek P. TNF-inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow-up study of patients with RA treated with etanercept or infliximab in southern Sweden. Ann Rheum Dis 2004;63:4-10.
4. Brennan A, Bansback N, Nixon R, et al. Modelling the cost effectiveness of TNF-{alpha} antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology (Oxford) 2007.
5. Kobelt G, Lindgren P, Lindroth Y, Jacobson L, Eberhardt K. Modelling the effect of function and disease activity on costs and quality of life in rheumatoid arthritis. Rheumatology (Oxford) 2005;44(9):1169-75.
6. Kobelt G, Woronoff AS, Richard B, Peeters P, Sany J. Disease status, costs and quality of life of patients with rheumatoid arthritis in France: the ECO-PR Study. Joint Bone Spine 2008;75(4):408-15.
7. Uhlig T, Heiberg T, Mowinckel P, Kvien TK. Rheumatoid arthritis is milder in the new millennium: health status in patients with rheumatoid arthritis 1994-2004. Ann Rheum Dis 2008;67(12):1710-5.
8. Hetland ML, Lindegaard HM, Hansen A, et al. Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. Ann Rheum Dis 2008;67(7):1023-6.
9. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364(9430):263-9.

10. Gulfe A, Kristensen LE, Saxne T, Jacobsson LT, Petersson IF, Geborek P. Rapid and sustained health utility gain in anti-TNF treated inflammatory arthritis. Observational data during seven years in southern Sweden. Ann Rheum Dis 2009 (March 2009, e-pub).
11. Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. Arthritis Rheum 2006;54(9):2784-92.
12. Maksymowych WP, Martin L, Russell S, et, al. Improvements in Health Related Quality of Life, Work Productivity and Resource Utilization with anti-TNF Therapies According to Funcational Status at Baseline: The Alberta Biologics Registry. EULAR 2009 2009;Abstract FR10563.
13. Karlsson JA, Kristensen LE, Kapetanovic MC, Gulfe A, Saxne T, Geborek P. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford) 2008;47(4):507-13.
14. van Vollenhoven R, Harju A, Brannemark S, Klareskog L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. Ann Rheum Dis 2003;62(12):1195-8.
15. Moots R, Kekow J, M C, et, al. Dose escalation accounts for differences in cost of care in 739 patients with rheumatoid arthritis with anti-TNF-agents: results from teh DART study. Ann Rheum Dis 2008;67(suppl II):330.
16. Augustsson J, Neovius M, Cullinane-Carli C, Eksborg S, van Vollenhoven RF. Rheumatoid arthritis (RA) patients treated with TNF-antagonists increase their participation in the work-force - potential for significant long-term indirect cost gains. Data from a population-based registry. Ann Rheum Dis 2009.
17. Fautrel B, Maravic M, Maurel F, et, al. Indirect costs of rheumatoid arthritis and their determinants. EULAR 2009 2009;Abstract THU0528.
18. Kobelt G, Lindgren P, Geborek P. Modelling cost and quality of life of treatment of RA with biological agents in clinical practice. Scand J Rheumatol 2008;in print (December 2009).
19. Kimel M, Cifaldi M, Chen N, Revicki D. Adalimumab plus methotrexate improved SF-36 scores and reduced the effect of rheumatoid arthritis (RA) on work activity for patients with early RA. J Rheumatol 2008;35(2):206-15.
20. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. Am J Med 2008;121(10 Suppl 1):S9-14.
21. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59(12):1690-7.
22. Wong J, Ramey D, Singh G. Long-term morbidity, mortality and economis of rheumatoid arthritis. Arthritis & Rheumatism 2001;44(12):2746-9.
23. Jacobsson LT, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol 2005;32(7):1213-8.

OCTOBER 2009

Gisela Kobelt, PhD MBA
Department of Orthopedics, Lund University (Sweden)
European Health Economics (France)
Gisela.Kobelt@he-europe.com

Frida Kasteng, MSc
i3 Innovus, Stockholm (Sweden)
Frida.Kasteng@i3innovus.com