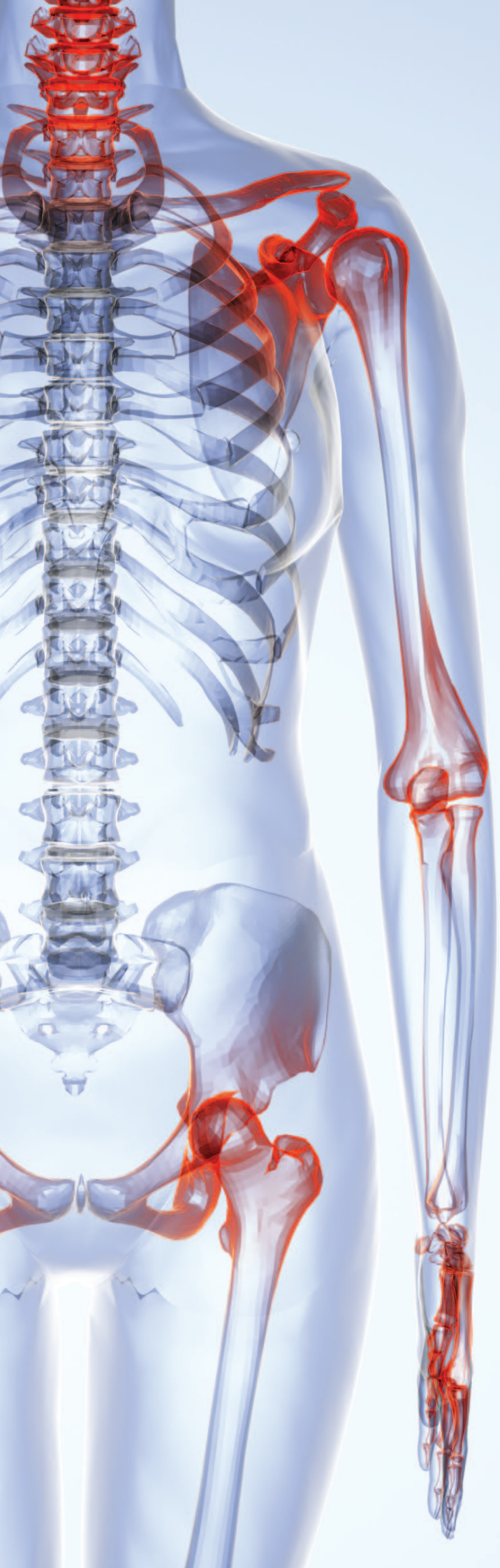

EUROPEAN HEALTH ECONOMICS

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Access to innovative treatments for rheumatoid arthritis in New Zealand. A comparison with Australia and the UK.

MAY 2010

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About European Health Economics

European Health Economics is a consulting company based in France founded by Gisela Kobelt in 1998. The company specializes in international economic evaluation projects for all types of medical interventions as well as education in health economics and economic evaluation. Projects have included all types of diseases, but a special focus has been on auto-immune diseases, in particular rheumatoid arthritis and multiple sclerosis. In addition to a number of book chapters and reports, Gisela Kobelt has 80 peer reviewed publications since 1996, of which 25 are in rheumatology (citation index 1350 not including own citations).

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- Sandra Kirby, Chief Executive of Arthritis New Zealand

Executive summary

The objective of this report is to assess the access to innovative treatment for rheumatoid arthritis (RA) in New Zealand and compare the results to Australia and the UK. The study builds on the previous work of *Access to innovative treatments for rheumatoid arthritis in Europe*. The prevalence of RA and the annual cost per patient was based on the methods developed in this previous work, accounting for difference between countries in demographic structure, price levels and health care expenditures. General data on costs, reimbursement systems, treatment guidelines, treatment effects and burden of RA from the previous European report were complemented with specific data for New Zealand and Australia, as well as a literature review and data from public sources and databases.

Burden of RA

The prevalence of RA was estimated at 0.53% in New Zealand and Australia, which is comparable to the UK (0.59%) and to other European countries with high prevalence rates. The burden of RA in terms of DALYs did not differ between the three countries and was driven mainly by effects on disability rather than mortality. The heavy burden of disability in RA is further illustrated when comparing the utility (quality of life) of different diseases where RA is associated with one of the largest decreases of utility, equivalent to for example the utility loss of multiple sclerosis.

Cost of RA

The annual average costs per patient diagnosed with RA in New Zealand and Australia were estimated to be 10,400 and 13,700 Euros (€), respectively, which is lower than the average cost of €15,000 per patient for Western European countries. Also, indirect costs constituted a larger proportion of total costs in New Zealand and Australia than in the UK. Direct health care costs in New Zealand were lower than in the two other countries, partly due to the lowest spending on biologics, explained by the highly restricted access to these therapies.

Uptake of treatments

The results of this analysis show very low usage of biologics in the indication of RA in New Zealand, noticeably lower than any of the Western European countries (E13) and also substantially lower than in Australia. Only an estimated 3% of the total patient population receives treatment with biologics, compared to around 9-10% in Australia and the UK, and 11% on average in the E13 countries. The E13 average is, however, low as a consequence of low usage in three markets with large patient population (Germany, the UK and Italy), while all but one of the other countries are well above 11%. Considering this, usage in New Zealand appears even lower than in other countries with similar economic conditions.

Determinants of access

No single factor can explain the difference in treatment access between countries. Although prices were on similar levels in the three countries compared, a lower spending per capita on health could suggest that New Zealand may have more difficulties to incorporate these treatments into the health care budget. However, the substantially

lower uptake in New Zealand, than observed in countries with comparable economic conditions, cannot solely be explained by these macroeconomic factors. Accepting that around 20% of RA patients are eligible for treatment with biologics, a mere 15% of these patients have access to them in New Zealand, compared to around 45-50% in Australia and the UK. Of the three countries, New Zealand has by far the most restrictive reimbursement for biologics in RA, with only one regimen currently reimbursed. PHARMAC, in contrast to reimbursement agencies in other countries, have found that TNF inhibitors do not represent good value for money. A larger number of RA patients per rheumatologist compared to Australia and the UK, as well as an administrative hurdle to access treatment may further add some explanation to the low up-take. Finally, treatment guidelines stipulate a start of biological treatment later in the course of the disease with no clear evaluation strategy of treatment response in New Zealand compared to the other two countries.

Value of treatment

It is still too early to evaluate the full effect of biological treatment. Nevertheless, a large number of individual findings and studies indicate reductions in all types of costs and significant increases in quality of life with biologic treatment, provided they are used for the right patients, at the right time and in the right way. Cost reductions are seen both in the short and long term. In the short term, direct costs will increase due to the cost of the treatments, but some parts 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 to society as a whole will occur in the long term, as patients remain in the workforce longer. The effect on quality of life is seen immediately after treatment initiation and a higher utility level is maintained while remaining on treatment. Biological treatments have shown to improve functional capacity and to lower disease activity, which are the main drivers of the effects on quality of life.

Conclusions

The clinical benefits of biologic treatment in RA in terms of the effect on inflammation, function and quality of life are widely accepted. Data is also emerging on lower usage of some resources such as surgical interventions, acute visits and work absence, but these short term savings do not truly off-set cost of the biologics. In progressive diseases, economic effects can generally only be observed in the long term, as patients do not progress to severe disability or do so later and remain in the workforce longer. In view of this, the views on the cost-effectiveness of biologics differ from country to country, leading to variations of restrictive use.

The European study found that uptake of biological treatments differed between countries with equal economic conditions, highlighting that access is determined by other factors than merely macroeconomic reasons. This finding is confirmed also for New Zealand and Australia. The results indicate that New Zealand provides the most restricted access to biologics for patients with RA.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, commonly presenting in middle life. The burden of the disease in terms of quality of life, loss of patients and costs to society are large, both in terms of health care costs and production losses. Treatment of RA is both symptomatic (corticosteroids, non-steroidal anti-inflammatory drugs [NSAIDs]) and targeted at the disease process (disease-modifying anti-rheumatic drugs [DMARDs]). Conventional DMARDs have been available since the 1980s. One of these, methotrexate (MTX), became the mainstay of RA treatment in the 1990s, with increasing use earlier within the disease course.

The late 1990s saw a revolution in the management of RA with the introduction of biological DMARDs. However, the side-effect profile of the treatments led to a cautious initial use. Many countries have therefore 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 increasing 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. More recent findings indicate that to avoid permanent functional limitations, these drugs should ideally be used as early as possible in the course of the disease. Still, the high associated costs of these treatments have hampered widespread use, with restrictions in patient eligibility for reimbursement in many countries. Patients had to have highly active disease despite treatment with two or 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. Other differences stem from price differences, the access to specialists, the level of insurance, the cost (price) in relation to wealth of countries and it is difficult to single out any of these factors as the major cause.

Earlier intervention will increase the number of patients eligible for treatment. The duration of biologics 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 modelling 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 a more severe disease status, associated with high social costs and low quality of life.

Early modelling 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 (HTA) agencies in few countries take a societal perspective. In this perspective, all costs regardless of who incurs them – the health care system, the patients, society as a whole – are taken into consideration. In the case of RA, as for other chronic progressive diseases, it is 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 the total cost of the disease.

Models predict high but acceptable cost effectiveness ratios for the biologics when used in the right patient population, 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, for whom a number of years of follow-up data are available, were the most severe cases with substantial irreversible disease consequences in terms of functional handicap and loss of work capacity. As more people who are eligible for treatment are on treatment, 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 line with this reasoning, a recent study has investigated the access to biological treatments in Europe: *Access to Innovative Treatments in Rheumatoid Arthritis in Europe 2009* (www.comparatorreports.se). This report investigated:

1. The burden of RA in terms of epidemiology and the effect on quality of life.
2. The cost of the disease, using a predictive cost model.
3. Uptake over time of biologic treatment and the number of patients treated.
4. 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.

This current report is an extension of the European report, adding New Zealand and Australia to the analysis. Comparisons in this report are mainly done between these countries and the UK. It uses the same methodology and presents selected results from the European report; hence some of the text will be overlapping. As Chapter 5 of the European report maps the current knowledge of the value of biological treatments without any country specific focus, this chapter is reproduced for ease of reference.

Chapter 1 – Burden of rheumatoid arthritis

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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 the burden for society, resulting from the number of people affected (prevalence). The economic burden will be discussed in the next chapter.

Previous research on the prevalence of RA in New Zealand and Australia give remarkably high prevalence estimates, compared to recent European estimates[1, 2, 3]. Since there is no documented reason for these differences, it was considered reasonable to base the prevalence estimation for New Zealand and Australia on data from comparable European countries. Consequently, this report is an extension of previous studies regarding prevalence of RA, and is to great extent based on a very recent European report ***Access to Innovative Treatments in Rheumatoid Arthritis in Europe 2009***[4]*, adapted to the New Zealand and Australian conditions.*

In this preceding European study, a standardized approach of estimating prevalence was used, based on two national datasets constituted by patients segmented by age and gender and with a definite diagnosis and follow-up for RA, that is, more than one contact with the health care system. This approach was adopted due to the apparent difficulty when estimating and comparing the proportion of the patient population on treatment with innovative treatments in different countries; literature gives conflicting data on the prevalence of RA, with numbers varying up to ten-fold. The average prevalence in the European population older than 19 years was estimated at 0.49%, based on the total number of patients in the EU 27 of slightly 2 million. Taking into account these results, two scenarios have been depicted for New Zealand and Australia - one based on the prevalence rates for northern Europe (referred to as upper estimates), and one for continental Europe (referred to as lower estimates), respectively. This lead to overall prevalence rate estimates in the adult population in both countries of 0.53 for the upper and 0.44 for the lower rates.

The burden of disease on patients - expressed as utility[A] - is one of the most severe (i.e. reporting low utilities) among chronic progressive diseases. The average utility in RA has been estimated at around 0.5 globally. However, more importantly, utility decreases from values close to normal to very low values (0.1-0.2) as the disease progresses to more severe health states with considerable functional impairment.

In conclusion, no accurate prevalence data to illustrate the burden of RA in Australia and New Zealand are available and proxy values from Europe have been imputed to the local population structure. There is no documented reason for rates being substantially different from Europe and these rates should be acceptable. Similarly, no local data on the burden to patients were found, but when the burden is illustrated as a loss of utility, the values can generally be directly transferred between countries. The severe impact of RA on patients' quality of life is well documented and is in our opinion fully applicable to New Zealand and Australia.

A Utility is a preference-based quality of life index anchored between 0, corresponding to death, and 1, corresponding to full health.

1.2 Prevalence

1.2.1 Background

Generally, the global prevalence of RA has been estimated at 0.5-1.0% of the adult population[5]. A review of studies published between 1988-2005, the majority of which was performed between 1998 and 2002, showed rates in Europe at 0.2-0.85%[B,6]. However, due to the 1987 revision of the criteria for classification of RA, allowing a more precise diagnosis excluding unspecified rheumatism, the prevalence appears to have decreased by 31% in women and 19% in men during a ten year period[7]. Also, since the introduction of biological treatments and their restriction to a defined group of patients, more focus is given to clear diagnosis, and the high number of "unspecified" cases may have further decreased. As a consequence, older studies of RA prevalence generally show a considerably higher prevalence than more recent studies.

Even though the globally commonly quoted prevalence of RA is about 1%[5], there are published studies reporting values ranging from 0.2% to 3.0%. Previous studies on the prevalence of RA in New Zealand and Australia report values at about 3.1%[1], 3.5%[3] and 2.5%[2], whereas others have reported values of 0.4%[C,8]. These published studies of prevalence have used different approaches, such as different populations, age groups or geographic areas within countries, self reported or diagnosed, limiting the comparability of the estimates. Also, some studies do not explicitly specify whether any limits were set. Thus, even the men-to-women ratios reported are likely influenced by these discrepancies in studies. Despite this, overall the studies concurred on a men-to-women ratio of 1:2 to 1:3.

The published prevalence estimates do, however, suggest a regional difference within Europe and it is commonly accepted that prevalence is higher in Northern Europe than in Southern Europe, even though there is no clear definition of where to set the boundary line. This is supported by the data review performed in our earlier report[4], which indicates that prevalence of RA is somewhat higher in the Nordic countries and the UK than in continental Europe. This may be due to differences in a range of factors, such as genetics, lifestyle, climate and the traditions of diagnostics and treatment of RA.

A number of reviews have focused on reporting results of prevalence estimates[6, 9-11], but no attempts have been made to adjust and extrapolate the numbers to different countries. However, this step is a prerequisite to estimating the total cost of RA, analyzing the uptake of biologics, and evaluating the proportion of patients on treatment. Consequently, the European report proposed an approach to estimated European prevalence rates, resulting in an overall prevalence rate of 0.49 in the adult European population. For comparability reasons, this approach will also be used in this current report since the main published prevalence rates for New Zealand and Australia are based on self reported prevalence, and hence do not fulfill the same criteria as the rates used in the European report.

1.2.2 Estimation of prevalence

Estimation of prevalence is a crucial issue in this study. First, the cost model developed to estimate the cost of the disease (Chapter 2) is based on three types of data: (i) the mean cost per patient based on available cost analyses adjusted for economic factors; (ii) total sales of biologic drugs in each country; and (iii) prevalence. The prevalence is used to estimate the proportion of patients treated in each country, in order to estimate the mean drug cost per prevalent patient, and subsequently extrapolate the mean cost per patient to total national costs. Second, all estimates of product uptakes (Chapter 3) are based on the estimated number of prevalent patients.

B For details of studies included in the referenced report, please see original reference or the European report

C Estimated by using number of prevalent cases over population data

In this report, the prevalence and cost of RA in New Zealand is mainly compared to the current situation in Australia and UK. Since the prevalence rates for New Zealand and Australia reported in available publications[1-3, 8] appeared unreasonably high or were not stratified into the categories necessary for the economic model, prevalence estimates by age and gender from the previous European report were applied instead[4]. Two prevalence sets were used, to serve as sensitivity comparators. One set is based on an average including the Nordic region (Denmark, Finland, Iceland, Ireland, Norway and Sweden) and the UK, and will be referred to as the *upper* prevalence set. The other set is an average of continental Europe (all remaining European countries), and will be referred to as the *lower* prevalence set [Table 1-1]. The rates were applied to the age and gender structure of each country [Figure 1-1] to estimate the overall prevalence in the adult population.

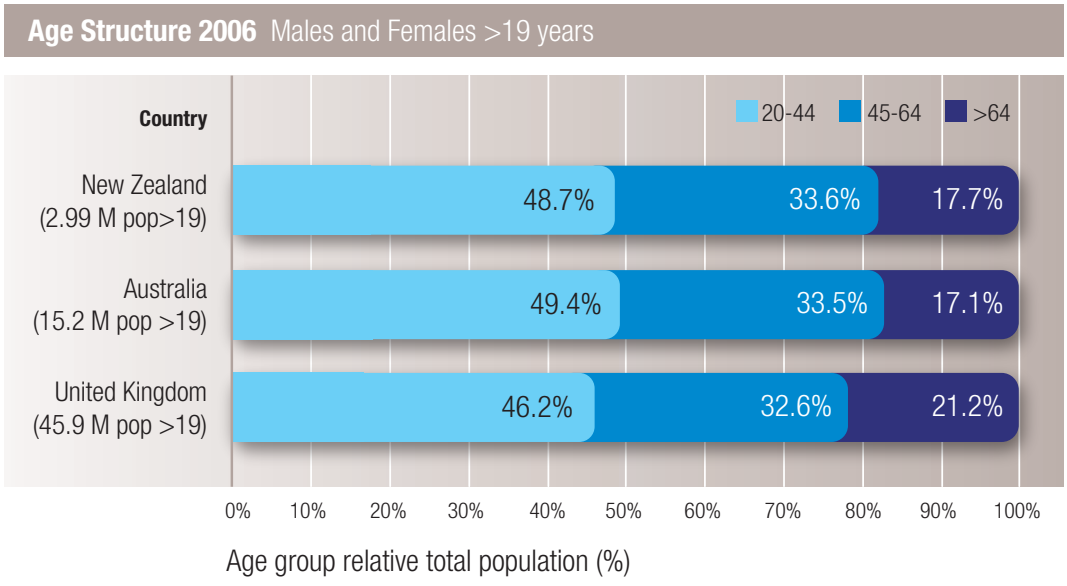
Table 1-1: Prevalence rates imputed and used for the calculations (% per adult population)

Age groups	20 – 44		45 – 64		> 65	
	Women	Men	Women	Men	Women	Men
Upper prevalence rates (Nordic region[i])	0.20	0.07	0.90	0.45	1.70	0.95
Lower prevalence rates (continental Europe[ii])	0.17	0.07	0.80	0.40	1.30	0.65

i Denmark, Finland, Iceland, Ireland, Norway, Sweden, UK

ii All other countries

Figure 1-1: Age structures for total population >19 years



Sources: Statistics New Zealand [http://search.stats.govt.nz]
Australian Bureau of Statistics [http://www.abs.gov.au/AUSSTATS]
Eurostat [http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home]

Based on the upper prevalence rates, the age and gender adjusted prevalence for the total population in New Zealand and Australia were estimated at 0.529% and 0.534%, respectively. The corresponding estimates for the lower prevalence rates were 0.435% and 0.438%, respectively. The overall prevalence in the adult population in the United Kingdom was 0.575%, indicating a higher age of the population. The total number of patients over 19 years was estimated at about 15,800 in New Zealand, 81,300 in Australia and 264,000 in the UK [Table 1-2] based on the upper prevalence estimates. This estimate for Australia is consistent with the one presented in an Australian report (80,976 patients, all age groups)[8]. This indicates that the imputation of the European prevalence estimates approximates the local data. The upper prevalence estimates will be used as the main scenario in this report. However, where helpful, comparison will be made to results based on the lower prevalence estimates.

Table 1-2: Estimated prevalence rates and number of patients (>19 years) applying the upper and lower prevalence rates, respectively

Country	Population >19	Patients >19		Prevalence >19 (%)	
	(000)	Upper	Lower	Upper	Lower
New Zealand	2,983	15,774	12,976	0.529%	0.435%
Australia	15,232	81,274	66,762	0.534%	0.438%
United Kingdom	45,871	263,672	NA	0.575%	NA

NA = not available

Figure 1-2: Estimated prevalence rates (upper prevalence)

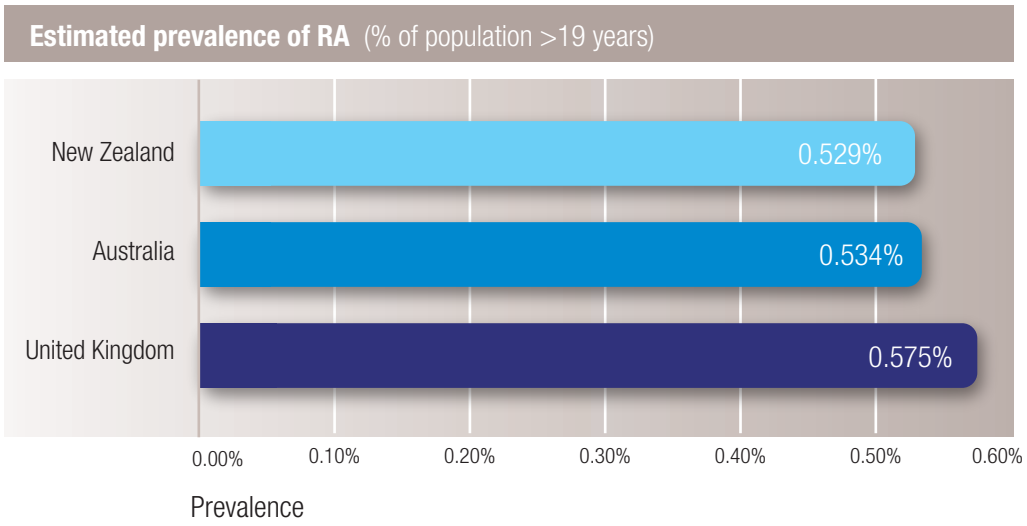


Figure 1-3: Estimated proportions of patients in different age groups (upper prevalence)

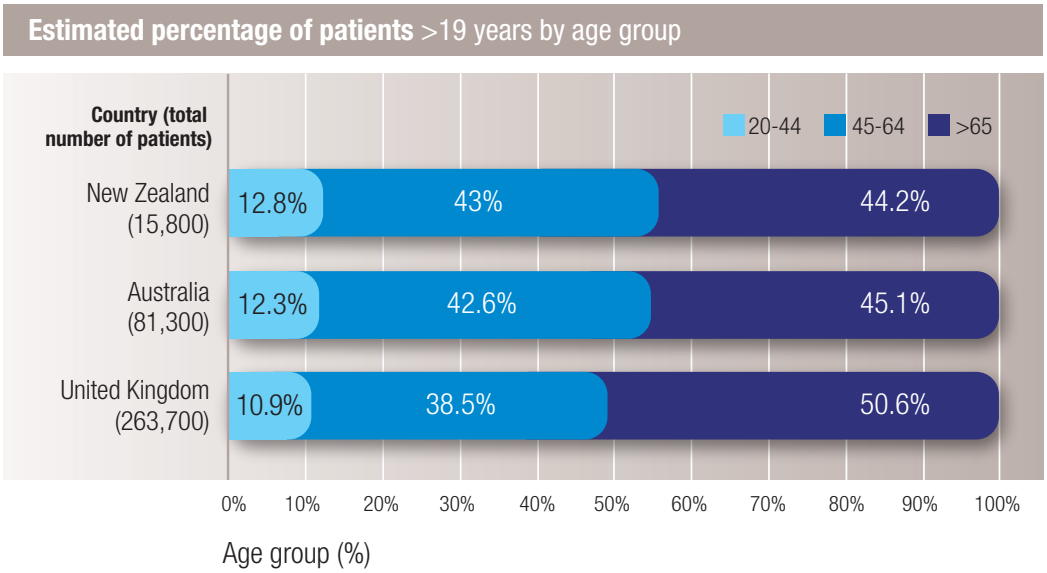


Table 1-3: Total estimated number of patients (upper prevalence)

Country	Total estimated number of patients by sex and age group						
	20 – 44		45 – 64		> 65		All ages
	Women	Men	Women	Men	Women	Men	Total
UPPER PREVALENCE SCENARIO							
New Zealand	1,517	500	4,567	2,210	4,806	2,175	15,774
Australia	7,413	2,601	23,112	11,468	25,155	11,523	81,274
United Kingdom	21,249	7,407	68,341	33,192	93,765	39,719	263,672
LOWER PREVALENCE SCENARIO							
New Zealand	1,290	500	4,060	1,964	3,675	1,488	12,976
Australia	6,301	2,601	20,544	10,194	19,237	7,884	66,762
United Kingdom	21,249	7,407	68,341	33,192	93,765	39,719	263,672

1.2.3 Comparison to published data

The results of the prevalence calculations in the European report, did not fundamentally differ from previously published estimates in most of the countries presented in that report[4]. In contrast, the estimates for New Zealand and Australia, using the methodology from the European report, are lower than previously published country specific estimates for New Zealand and Australia. These latter estimates [Table 1-4], published in reports by Access Economics and the Ministry of Health in New Zealand[1,2,3], are based on surveys of self reported prevalence which is not necessarily equivalent to patients with confirmed diagnosis, explaining the discrepancy in estimates. Nevertheless, there is one report by Begg et al[8], that presents prevalence data for Australia similar to estimates in this current report. The difference between the two estimates lies in the population base - adult population in this report compared to the whole population in the published report by Begg[8]. The average prevalence in Europe was estimated to 0.49, which can be compared to the estimated prevalence in New Zealand and Australia at approximately 0.53 (upper prevalence) or 0.44 (lower prevalence).

Table 1-4: Comparison of estimates to published data

Country	Year	Estimated prevalence, %	Published prevalence, %	Population Age	Reference
Australia	2003	0.53	0.4[i]		8
Australia	2007	0.53	2.5		2
New Zealand	2006-07	0.53	3.5		3
New Zealand	2002-03	0.53	3.2	≥15	1
UK	2002	0.57	0.85[ii]	≥16	12

I estimated from number of prevalent cases and population data

ii crude rates

1.3 Health burden

In this report *Health burden* is defined as the impact on the health of patients, related to quality of life and their ability to perform daily activities. On a macro level, health burden is generally measured by Disability-Adjusted Life Years (DALY), which enables comparison across diseases. This is a two-dimensional measure developed by the World Health Organization (WHO)[D], integrating mortality and morbidity (disability). It is calculated as the sum of years of life lost (YLL) and years lived with disability (YLD), weighted according to the severity of the disease[13]. One DALY can be interpreted as the loss of one year of healthy life.

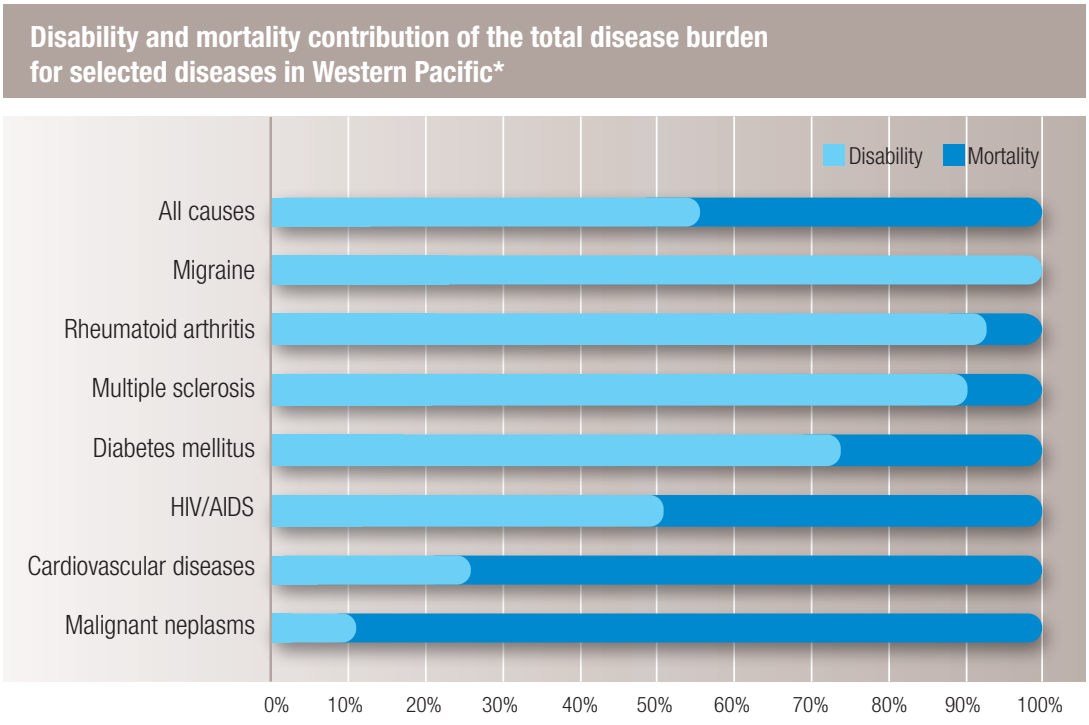
In health economic studies, the Quality-Adjusted Life Year (QALY) measure is preferred. It is a two-dimensional measure that accounts for both quantity and quality of life lived. It is mainly used to assess the value of medical interventions, and is based on the number of life years that would be added by the investigated intervention[14] and at what quality the added life is lived. Each life year lived is weighted with a utility value between 0 (corresponding to death) and 1 (corresponding to perfect health), which represents the preference of the population for the examined health states[15]. There are established methods for the measurement of utility as a parameter between 0-1, with reference values clearly anchored to the general population[16]. The QALY measure differs from the DALY by taking into account the subjectively experienced health related quality of life of an individual (i.e. utility)[16].

D www.who.int

1.3.1 DALYs in RA

By investigating the contribution of years of life lost (mortality) and years lived with disability (morbidity), measuring the number of DALYs lost is commonly used to compare the burden of disease between different disease states. However, the distribution between mortality and disability varies greatly depending on the type of disease, as exemplified with Western Pacific data in Figure 1-4. For RA, the greatest share of the disease burden is caused by disability (approximately 93%), whereas for conditions such as cancer and cardiovascular diseases, premature death constitutes the largest part of the disease burden. The number of DALYs for RA are estimated at 74, 71 and 83 per 100 000 population (age adjusted) for New Zealand, Australia and the UK, respectively.

Figure 1-4: The share of disability and mortality in the disease burden in the Western Pacific region A



Source: WHO, Department of Measurement and Health Information;

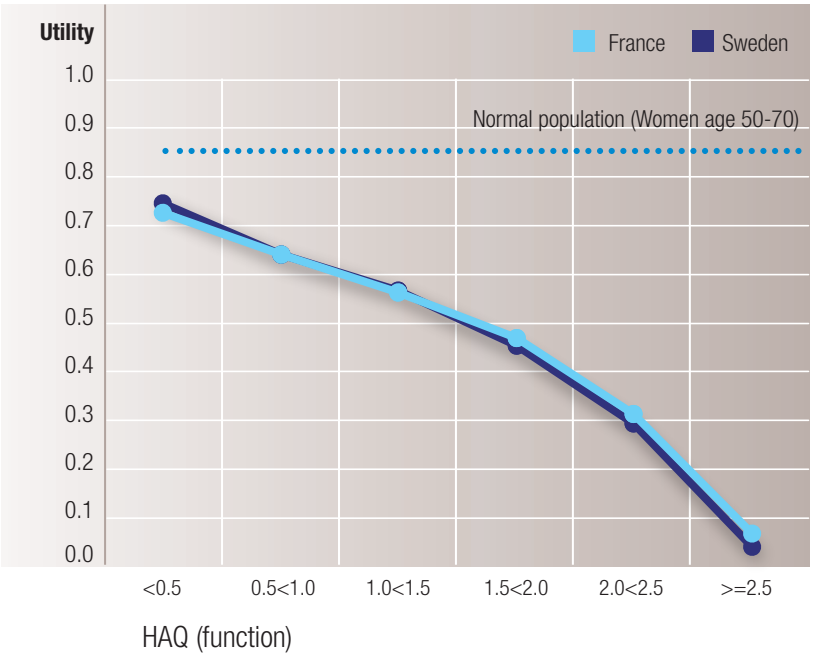
*WHO subregion WPR A (Australia, Brunei Darussalam, Japan, New Zealand, Singapore)

1.3.2 QALYs in RA

QALYs have been widely used and accepted for economic evaluation in RA. As the disease is characterized by diverse symptoms, such as swollen and tender joints, stiffness, pain, fatigue, and temporary and irreversible functional disability, quality of life appears the most appropriate measure of the disease burden and the potential health gain achieved by treatment. A lower utility indicates a worse health related quality of life of the patient, which is also correlated to increased work absence and use of health care resources for RA patients (discussed in detail in Chapter 5).

The utility value is closely correlated with functional capacity, assessed through the Health Assessment Questionnaire (HAQ) [Figure 1-6]. A considerable number of studies have shown that the utility value decreases rapidly immediately from the onset of the disease[17-22]. Early in the disease, HAQ is most strongly influenced by the inflammatory symptoms (swollen and painful joints, together with fatigue), whereas both inflammation and impaired physical mobility due to irreversible joint erosion predominantly impact the health assessment later during the disease progress. In addition to functional capacity, disease activity exerts an effect on utility. Patients with higher disease activity have lower utility scores than patients with lower disease activity, even though they may have identical HAQ levels[21]. Additionally, the degree of inflammation of the disease, the pain and the fatigue scores measured using Visual Analogue Scales (VAS 0-10) have been shown to correlate with HAQ scores[22]. The mean utility value is thus strongly influenced by the disease severity of the sample population, whereby small patient samples may produce biased results.

Figure 1-5: Utility related to disease severity in RA



Source: Adapted from[17, 21, 22]; Utility was measured in both studies using the EQ-5D.

Furthermore, measurement of utility using the EQ-5D questionnaire is currently included in some registry follow-up processes of patients on treatments with biologic drugs. The first results of these measurements are available from the Southern Swedish Registry (SSATG)[23] (further details in Chapter 5).

In comparison to many other chronic diseases, the mean utility in RA is low, as shown in Table 1-5. Comparing the mean utilities of patients with RA to the utilities of an age-matched sample of the total population, the loss of QALYs is estimated at 0.2-0.3 QALYs per year, which equates to a 20-30-% loss of quality of life compared to perfect health[22].

Table 1-5: Utilities in different chronic diseases

Disease	Mean utility	Sample size
Other rheumatoid arthritis[i]	0.43	120
Rheumatoid arthritis[ii]	0.50	1,487
Multiple sclerosis[iii]	0.56	13,186
Angina pectoris	0.58	284
Acute myocardial infarction	0.61	251
Atrial fibrillation and flutter	0.61	189
Chronic ischaemic heart disease	0.64	789
Non-insulin dependent diabetes	0.67	159
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
Ulcerative colitis	0.79	61

i ICD code M06; Source: Orme et al[24] (original data from from Currie et al[25]), except:
ii Kobelt et al[22]
iii adapted from Kobelt et al[26]

1.4 Conclusion

This chapter estimates the prevalence of RA and summarises the literature on the burden of the disease in New Zealand, Australia and the UK. The prevalence rates for New Zealand and Australia are somewhat difficult to assess from published sources, due to different measurement techniques, resulting in values that are considerably higher than rates in the countries with the highest prevalence in Europe (the Nordic region and the UK). Therefore, in this report the prevalence rates from the European report were used for New Zealand and Australia instead, resulting in similar prevalence rates in the countries compared within this study. The prevalence rates reflect the prevalence of patients with confirmed diagnosis rather than the potential number of patients, as this is more relevant when estimating the proportion of patients receiving treatment and utilising health care.

Data on health burden of the disease are consistent and can be applied across countries. As noted in this chapter, the DALYs of RA fell within a narrow range for the investigated countries. The burden of RA in terms of DALYs is, in comparison to other diseases such as e.g. cancer, driven by effects on disability rather than mortality. This also translates into large effects on health related quality of life (utility) compared to other common diseases, significantly impairing the life of patients with RA.

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Chapter 2 – Cost of rheumatoid arthritis

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2 Cost of rheumatoid arthritis

2.1 Summary

In this chapter, the total costs of RA in New Zealand and Australia are calculated based on the average cost per patient and on the prevalence of diagnosed patients, as estimated in Chapter 1.

The published literature on cost of RA in different countries does not give a clear picture, as studies are not consistent in their approach and in the cohort and data included in their analyses. This was the case when evaluating the costs of RA in New Zealand and Australia as well. In chronic diseases, however, 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 in order to extrapolate the cost per patient to total national costs of RA. In the absence of such data, age is used as a measure for disease severity.

The same age groups are applied as for the calculation of prevalence in the previous chapter, since this grouping takes into account the differences particularly in workforce participation and income. In the main analysis, cost data for New Zealand and Australia were imputed using the method from the European cost model, while UK data was taken directly from the recent European report. In an alternative scenario, the costs for New Zealand and Australia were instead based on two previous extensive reports by Access Economics. An exception was the cost of biologic treatments, for which the actual cost per patient was extracted from international sales data. Subsequently, the calculations were made in accordance to the cost model used in the recent European report.

In the main analysis, the annual average costs per patient diagnosed with RA in New Zealand and Australia were estimated to be €10,400 and €13,700, respectively, using the prevalence rates from Northern Europe. This is lower than the average cost of €15,000 per patient estimated for Western European countries. The total cost for RA was estimated to €163.8 million and €1.1 billion in New Zealand and Australia, respectively. When using the local cost data, total costs were considerably lower, and the proportions of costs due to different types of resources changed considerably. Costs in New Zealand were almost entirely due to informal care and production losses, with direct healthcare costs almost disappearing. Of the three countries, New Zealand had the lowest proportion of costs for biologics.

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 healthcare system, and the indirect costs for resources lost due to morbidity (disability) and premature death (mortality). The considerable cost of RA, both to the health care system and to society at large, 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 by a certain degree of uncertainty. A number of factors influence the results, such as the country where the study has been performed, the study objectives, the

cohort included, prevalence estimates, and not least, the methodology applied[1]. Major methodological issues in cost-of-illness studies pertain to (i) how costs that are directly related to the disease can be separated from unrelated costs that arise due to any co-morbidity and (ii) which perspective is adopted for the analysis - a societal perspective (all costs regardless of who pays), or a payer perspective (costs exclusively carried by the healthcare and social systems). The largest differences will be due to the perspective applied, although even within studies applying the same perspective, notable differences may arise due to the method of calculation chosen – in particular the evaluation method of production losses [Table 2-1].

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

	PERSPECTIVE France[2] Annual cost per patient (N=1487; €2005)		CALCULATION METHOD Netherlands[3] Annual indirect cost per patient (N=576; €2005)	
	Public payers[i]	Societal	Human capital method	Friction cost method
	Mean (SD)	Mean (SD)	Mean	Mean
Direct medical costs[ii]	9,216 (15483)	11,757 (17,615)		
Direct non-medical costs[iii]	136 (702)	4,857 (11,827)		
Indirect costs[iv]	2,305 (5178)	5,076 (11,253)	278 ± 1,559	4,434 ± 9,957
Total annual cost	**11,658 (16,834)**	**21,690 (26,238)**		

i Excluding complementary insurance (Mutuelles)
ii Health care costs
iii Investments, services, transport, informal care
iv Production losses, patients <60

Nonetheless, studies concur that 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, in most studies of RA, production losses represent the largest cost. More recently, attention has been paid to the large costs borne by patients and their families that arise due to the need of adapting the living environment, or for aids for everyday life 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 expected in the case of chronic progressive diseases, there is a strong correlation between cost and disease activity, severity, duration, age, and functional status. However, functional status, (as measured by the Health Access Questionnaire, HAQ) is by far the strongest driver of cost.

Even though information about the cost of a disease provides important general information to policy makers, it cannot be used directly for decision making concerning resource allocation to individual treatments within a therapy area. 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, the average cost per patient increases with increasing functional disability (and thus with age). Therefore, economic evaluation contributes to estimation of long-term consequences of changing the course of the disease, and thereby prevention or delay of the development of severe disability[1].

2.3 Modelling the cost of RA

Costs in health economics are divided into direct and indirect costs:

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

These definitions are used in most studies. Nevertheless, there is some discussion whether informal care should be considered a direct or an indirect cost. Informal care costs can be estimated in three different ways: based on (i) opportunity costs (production losses) for carers included in the labour force, (ii) replacement cost of professional carers, or (iii) loss of leisure time for all categories of carers. Access to data on informal care is often rather limited, and so the cost model used in the European report was designed to manage and report informal care as a separate item. Other non-medical costs, such as transportation, social services, etc., are integrated in direct costs.

To diminish any influence of different estimation methods in original publications, costs of RA in New Zealand and Australia were estimated using the method for imputing values, which was developed in the European cost model. These estimates were based on the upper prevalence estimates, with sensitivity analyses done on the lower prevalence rates (Chapter 1). In an alternative scenario, also based on the upper rates, national published sources for costs were used instead, and applied within the European cost model.

2.3.1 Model design

This study could be described as a prevalence-based cost-of-illness study that uses a cost model that estimates total annual costs for a prevalent patient population, based on the mean annual cost per patient. The cost model was developed in earlier works[10, 11,] and allows estimating cost of RA despite a considerable lack of data. The model imputes data on the cost per patient from published studies and reports, as well as comparative economic indices, to estimate costs where cost data are missing or incomplete. Subsequently, the estimated costs per patient are combined with the country-specific prevalence to obtain the total cost of RA for each country included in the study. This enables the comparison of RA costs across different countries.

The mean annual cost per patient can be estimated using either aggregated resource consumption from available statistics, or by collecting actual resource consumption in a representative sample of patients. In this study, costs were divided as described above, into medical costs, costs for biologics (drugs) and non-medical costs, informal care, and indirect costs (production losses). Non-medical costs were further separated into services (formal help in the home, transportation) and products (aids, devices, adaptations, other). In a first step, available annual costs per patient for each of these categories were extracted from available sources. In a second step, these costs were inflated to the same base year (2008), using country specific consumer price index (CPI), and adjusted for different price levels between the countries. In a last step, costs were adjusted into common currency (Euro), using trailing-twelve-month (TTM) exchange rates for 2008 (2.06 NZD/EUR and 1.72 AUD/EUR). Where data was missing, costs were imputed based on the cost model.

The prevalence of RA was estimated in three age groups, namely 20-44 years, 45-64 years, and >64 years (Chapter 1). Thereafter, total costs were calculated for the same age groups. This division into age segments allows a more precise calculation of costs, in particular production losses, as salary levels tend to differ between the first two groups, and are absent for retired patients, the majority of which are included in the >64 group.

The retirement age in New Zealand and United Kingdom is 65 years[E], while Australia has no statutory retirement age, but a span from 55 to 70 years, on recommendation by the retirement income system[F]. This study uses 65 as the generally accepted retirement age, which gives a good approximation.

2.3.2 Model data

2.3.2.1 Cost data and assumptions

A literature review was conducted to identify studies relevant for the purpose of this cost study. PubMed and reports from various research institutes were included in the queries. Secondly, costs were separated into the categories mentioned above, which is direct costs including medical costs, cost for biologics (drugs) and non-medical costs, indirect costs (productivity losses) and costs for informal care.

The cost data for the alternative scenario in this report was mainly extracted from two previous reports on the economic impact of arthritis in New Zealand and Australia, respectively[12, 13]. These studies have not stratified all costs by arthritis type, creating a certain degree of uncertainty when assessing the total RA related costs. Additionally, the reports raise their own concerns as to the uncertainty of their estimates where data have been missing or assumptions have been made. As these costs have been assessed by different estimation methods compared to the cost studies qualifying for the European report, it limits the comparability between countries. As discussed in Chapter 2.2, different estimation methods have notable impact on the end results. Cost estimates based on these data are therefore presented in an alternative scenario, whereas imputed values were used in the main scenario.

To fit the New Zealand and Australian data to the cost model for the alternative scenario, the total RA cost estimates were divided with the upper prevalence rates from Chapter 1. Additionally, a few assumptions had to be made to get the RA related costs:

1. The report on access to RA treatment in New Zealand[12] presents estimates of the costs of informal care based on both the replacement cost method by arthritis type (24.1% attributable to RA), and costs based on the opportunity cost method, but only presented for all arthritis types compounded. To be comparable to the European estimates, the costs estimated by the opportunity cost method were used, of which 24.1% were assumed to be attributable to RA, based on the RA proportion of the informal care costs estimated by the replacement method.
2. Regarding the indirect costs, these were also not separated by arthritis type in the New Zealand report; hence the same proportion (24.1%) of RA-to-all arthritis was applied.
3. In New Zealand 4.6% of all arthritis inpatient costs were attributable to RA. In absence of any division into arthritis types of other cost items within direct costs, this figure was applied, probably underestimating the total direct costs attributable to RA.
4. Regarding informal care and indirect costs in Australia, data were available only for all arthritis compounded[13]. In this case, the proportion used to calculate the costs accounted for by RA was based on the contribution of RA to the total direct health expenditures of arthritis (9.9%).
5. For calculations of the labour force participation and employment rate in New Zealand, data specifying age and gender distribution in combination was unavailable. Therefore, it was assumed that the male-to-female ratio is constant throughout all age segments. The same gender ratio was applied also to the Australian data.

E http://direct.gov.uk & www.pharmac.govt.nz
F www.aihw.gov.au

The cost data taken from the national sources was also adjusted according to currency exchange rates, inflation rates and price levels. All costs were updated to 2008, since more recent data (for 2009) were still unavailable for several cost types, and also in order to keep the results comparable to the results presented in the European report (published October 2009). The cost of biologics is based on IMS data for both the main and alternative scenario, further described in Chapter 3 of this report.

2.3.2.2 Economic comparative data

Regarding New Zealand and Australia, data on health care expenditure were taken from WHO, labour costs were obtained from OECD, price levels were extracted from the World Bank, and population statistics concerning demography and employment were obtained through the national statistics agencies in New Zealand[G] and Australia[H], respectively. Regarding data on European countries, especially the United Kingdom, data refer to the previous report on access to innovative treatments in Europe[10]. Based on these data, comparative indices have been computed in line with the cost model. The data is presented in Table 2-2 and Table 2-3. The health price levels in New Zealand and Australia were in line with Western European countries (refer to the European report[10] for further information). In contrast, for the health expenditure per capita index, both countries (especially New Zealand) were in the lower end compared to Western European countries (e.g. Norway 143, France 137, Germany 136, Sweden 116, Spain 98 and Italy 84[10]). The indices for labour costs place New Zealand and Australia are on comparable levels to Mediterranean Europe[10].

Table 2-2: Relative prices and relative health care expenditures per capita in the countries included

	Comparative price level index Health 2007 (EU27=100)	Health expenditure per capita 2005 (PPP€)	Comparative health exp per capita index (EU27=100)
EU27	100	1,754	100
New Zealand	107	1,520	87
Australia	119	1,821	104
United Kingdom	117	1,778	101

Table 2-3: Labour costs and employment rate by age as of 2006

	Monthly labour cost EU27		Monthly labour cost EU27		% employed		% employed	
	All branches		Health and social work		(20-44 yrs)		(45-64 yrs)	
	€ 2006	Comparative levels (EU27=100)	€ 2006	Comparative levels (EU27=100)	women	men	women	men
EU27	3,117	100	2,723	100	68.0%	83.0%	54.0%	71.0%
New Zealand	2,524	81	2,074	76	70.0%	84.2%	69.8%	83.9%
Australia	3,367	108	2,672	98	65.9%	80.9%	65.7%	80.6%
United Kingdom	:	137	4,258	156	72.1%	86.0%	63.4%	76.8%

G www.stats.govt.nz
H www.abs.gov.au

2.3.3 Results

This study estimates that there are approximately 15,800 patients who have been diagnosed with RA in New Zealand (13,000 using the lower prevalence scenario), which corresponds to a prevalence rate in the population older than 19 years of 0.529. The number of patients in Australia is estimated to 81,300 patients (66,800 by lower prevalence scenario), giving a prevalence rate of 0.534, conclusively very close to that of New Zealand. The corresponding figures in the UK are 262,700 patients in total, and a prevalence rate of 0.575.

The total cost of RA in New Zealand was estimated at €163.8 million annually, which corresponds to an annual average cost per patient of €10,400 (10,700 using the lower prevalence). The corresponding figures for Australia are €1.1 billion in total costs and €13,700 per patient (14,000 for the lower prevalence), respectively [Table 2-4]. These per patient estimates can be compared to those of Spain, Italy, the UK, Sweden and Austria at values of 9,900; 11,460; 12,000; 13,000 and 13,800 respectively[10].

Similar to previous studies, it was found that costs outside the health care sector dominate the total costs; production losses (indirect costs), informal care and non-medical costs are often only partially reimbursed [Figure 2-1].

Table 2-4: Estimated annual costs of RA

	per country (Euro 2008)		per patient (Euro 2008)				
Country	Total prevalent cases of RA	Total cost of RA	Total per patient costs	Direct cost (excl.biol)	Biologics	Indirect cost	Informal care
United Kingdom	263,672	3,163,265,560	11,997	5,265	888	3,008	2,837
New Zealand	15,774	163,839,473	10,386	4,042	361	4,327	1,656
Australia	81,274	1,109,896,043	13,656	4,903	1,145	5,395	2,214
Western Europe	1,581,350	23,716,124,129	14,997	6,345	1,285	5,012	2,355

Figure 2-1: Structure of costs

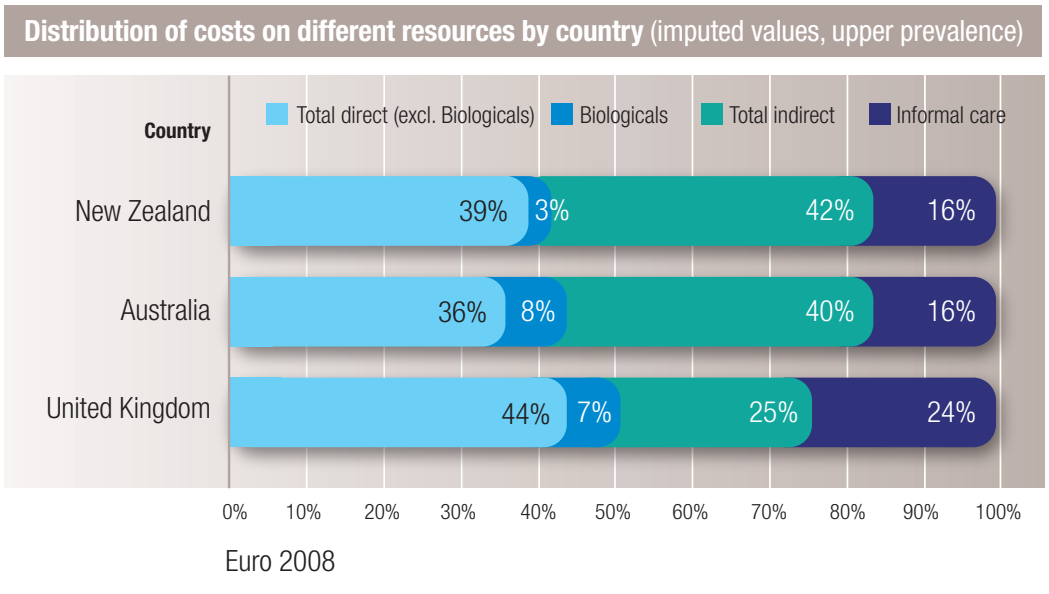
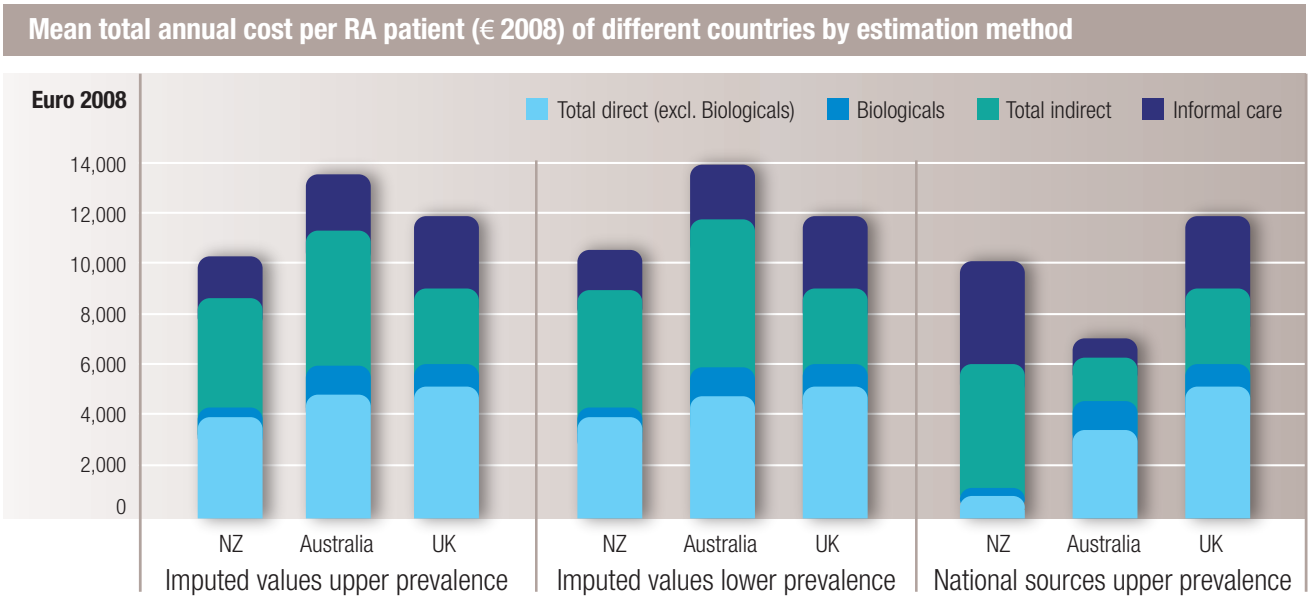


Figure 2-2 depicts the differences in results by estimation method. The methods compared are imputed values based on the upper prevalence rates, lower prevalence rates and national values based on the upper prevalence rates.

The results indicate that specifically the cost structure for New Zealand is dependent on which source is employed, although remaining on a similar total level. The total costs for Australia decreases when using the national sources, mainly due to changes in the indirect costs.

Figure 2-2 Comparison of total cost between countries by estimation method



Note: UK does not change with method as they are taken from the European report.

2.4 Conclusion

In this chapter, the costs of RA in New Zealand and Australia have been estimated using a method developed for estimating the cost of RA in Europe. With this method, available published literature is used to estimate the average cost per patient where available and imputing values to countries with no data using economic and health indicators. Total cost is estimated by applying the average cost per patient to each country's gender and age-specific prevalence of diagnosed patients.

Although some national sources for costs for New Zealand and Australia were available, these had a number of methodological issues that made them less appropriate to use, particularly in a comparative study. The main estimates in this chapter are thus based on the imputation method using European data, and an alternative scenario with the local data is presented.

With the imputation method, costs are rather similar to the UK, with New Zealand slightly lower and Australia slightly higher. The difference is mainly due to the cost of informal care. When the local data are used, costs in Australia are substantially lower, but the proportions remain similar. Contrary to this, for New Zealand, direct health care costs become essentially non-existent and the vast majority of costs are due to informal care and production losses. For a disabling disease such as RA, this scenario seems an unlikely representation of costs. The much lower costs in this scenario may however be explained partly by the fact that the New Zealand and Australian national reports present total costs for the whole arthritis population rather than cost per patient, and partly because they used a much higher prevalence. In view of this, we would argue that the imputed values most likely present a more realistic estimate.

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Chapter 3 – Uptake of biologic treatments

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Figure 3-6 Proportion of prevalent RA patients treated with etanercept, upper prevalence estimate 36

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Figure 3-13 Proportion of prevalent RA patients treated with rituximab, lower prevalence estimate 40

3 Uptake of biologic treatments

3.1 Summary

This chapter provides a description of current access to biologics in the indication of RA. In the absence of readily available information on the number of patients treated in each country, we have used international sales data from IMS on volume (mg) and annual drug doses to estimate the number of patients on treatment. This was then related to the prevalence estimated in Chapter 1 to calculate the proportion of patients treated. In addition, average sales per prevalent patient were estimated from the sales data in value (in € for the purpose of comparison), the number of patients treated and estimated prevalence.

Results are presented as uptake curves representing the proportion of prevalent patients treated and drug sales (€) per prevalent patient, for biologics as a group and for each individual treatment.

Overall, the results of this analysis show very low usage of biologics in the indication of RA in New Zealand, far lower than in any of the Western European countries included in the E13 summary figures, and also substantially lower than in Australia. Only 3% of the total patient population was estimated to receive treatment with biologics, compared to around 9-10% in Australia and the UK, and 11% on average in the E13 countries. If we add to this the fact that the E13 average is low as a consequence of low usage in three markets with large patient population (Germany, the UK and Italy), while all but one of the other countries are well above 11%, usage in New Zealand appears even lower than other countries with similar economic conditions.

A further difference is that in New Zealand only one product is currently reimbursed by the national funding body PHARMAC, and not having a choice of product, or the possibility to switch to another product when response is deemed insufficient, may lead to suboptimal treatment. It is, however, not possible to say whether further inclusions in the reimbursement list would improve access or whether this would only allow patients currently treated, but with limited effect, to switch to another product.

3.2 Methods

To assess the access to therapies, information on the number of patients treated in each country and for what indication is needed. This information is, however, not readily available. As in the European report, IMS data on the total volume in mg and the annual mg required for an average patient according to the label have been used to estimate the number of treated patients. This estimate can then be related to the prevalence rates from Chapter 1 to estimate the proportion of patients treated. Finally, using IMS data on total sales, adjusted for the proportion of sales for the indication of RA, allows estimating average cost per prevalent patient. Calculations were performed for biologics as a group and by individual product.

In view of the need to impute prevalence estimates from Europe to New Zealand and Australia rather than using local prevalence data as discussed in Chapter 1, results are presented for both the upper and lower prevalence estimates.

3.2.1 Data

Despite a number of shortcomings, IMS data are currently the only source of comparative data at an international level. It is likely that in no country are 100% of the sales captured, but it is difficult to accurately quantify 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. However, IMS data are a solid source in most countries for international comparison purposes.

IMS data is limited to retail sales in both countries and does not capture direct merchandising as well as direct hospital sales. This likely underestimates total sales slightly. However, considering that, for example in New Zealand, retail and direct hospital sales constitute only 2.5% of total sales[1], the difference may not be very large.

Only one biologic is reimbursed for RA in New Zealand (adalimumab), starting in 2005. This year was therefore set as cut-off for the IMS data extraction for both New Zealand and Australia for comparability. However, in the Australian market several biologics were used prior to 2005. Thus, uptake curves for New Zealand represent usage from the time of reimbursement, while the curves for Australia do not cover early usage.

3.2.2 Treatments

The first biologic treatment for RA registered in New Zealand and Australia was infliximab, followed by etanercept, adalimumab and anakinra (Australia only), and more recently abatacept. The three TNF inhibitors etanercept, infliximab and adalimumab have subsequently been approved for further indications: ankylosing spondylitis, psoriatic arthritis, psoriasis, juvenile arthritis, Crohn's disease and ulcerative colitis. Anakinra and abatacept are exclusively used for RA, but anakinra has not been licensed in New Zealand. Thus, with the exception of rituximab which was first licensed for Non-Hodgkins Lymphoma, all biologics used for RA had their first license issued for RA.

Recently, tocilizumab, golimumab and certolizumab pegol have gained (or are about to gain) market approval for RA, but are not yet listed under the reimbursement schemes in New Zealand and Australia. None of these treatments were used during the period covered by our data.

Generally the biologics were approved somewhat later in New Zealand and Australia than in Europe (EMEA approval)[2].

Table 3-1: Year of regulatory approval for RA

	New Zealand	Australia	Europe (RA)
Infliximab	2000	2000	1999
Etanercept	2002	2003	2000
Adalimumab	2004	2003	2003
Anakinra	-	2003	2001
Rituximab	2007	2006	2006
Abatacept	2008	2007	2006

Sources: New Zealand www.medsafe.govt.nz; Australia www.ebs.tga.gov.au

Although drugs are priced at comparable ex-factory levels, the end-user prices differ between countries dependent on wholesale and retail margins, as well as confidential rebates and pricing agreements between manufacturers and payers[2]. Generally adalimumab, etanercept and abatacept have similar prices (€13-14,000/year), although slightly lower in New Zealand (at €11,000/year). Infliximab and rituximab are priced lower at label dosing (approximately €9,000). However, usage data of infliximab in clinical practice indicate that slightly higher doses are often used, bringing the total cost of infliximab, including infusion costs, to a similar level as the other TNF inhibitors.

If more frequent administrations (>2 per year) are required, the cost of rituximab also increases. Assuming higher doses for either of these two drugs would lead to a decrease in the number of patients receiving treatment in estimations presented below in Chapter 3.3.2.

The reimbursement of biologics differed between the two countries: In New Zealand, only adalimumab is reimbursed for the treatment of RA by the government drug funding agency PHARMAC. In Australia, all biologics listed above are subsidized for RA on the pharmaceutical benefits scheme (PBS). (Reimbursement systems are further discussed in Chapter 4.5)

3.3 Results

To allow comparison with the European data, prices are expressed as Euro. Results for the drugs included, three TNF inhibitors and rituximab, are presented for the upper and lower prevalence estimates, as

- the total number of patients treated
- the proportion of patients on treatment
- the mean cost per patient

3.3.1 Use of biologics in the indication of RA

As mentioned above, with the exception of abatacept and anakinra, all biologic treatments used in RA are approved for other indications as well. The proportion of each drug used in RA is not available from IMS data or any other accessible database and is likely to differ between countries. Due to the absence of such precise data, an overall estimate was used for Europe. For New Zealand and Australia, each individual drug's proportional use in RA was estimated by Roche Australia and Roche New Zealand for each year, and used directly in the analysis of uptake.

It should be noted that no sales were reported for anakinra and abatacept in New Zealand. For etanercept, no sales were reported for RA, although it is reimbursed for juvenile idiopathic arthritis (JIA). If these patients develop RA they may continue to receive etanercept. 10-20% of the prescriptions of etanercept are for JIA and may hence include some RA patients as well. However, as our analyses used prevalence estimates for the adult population, thus de facto excluding juvenile arthritis patients, we left usage of etanercept in RA at zero. Infliximab is not reimbursed in New Zealand and rarely used, hence the proportion used in RA was also set to zero. Off label use of infliximab and etanercept is assumed to be minor because of the high costs associated to the treatments. Consequently, usage of the third TNF inhibitor, adalimumab, in RA was high compared to Europe. The penetration of rituximab was lower than in Europe due to the more recent approval for RA.

The estimates of the proportion of each drug used in RA are shown below.

Table 3-2: Proportion of drugs used in the indication of RA

	New Zealand	Australia	Europe[2]
Etanercept	0%	63%	65%
Infliximab	0%	31%	45%
Adalimumab	100%	72%	65%
Anakinra	-	100%	100%
Rituximab	2%	5%	10%
Abatacept	-	100%	100%

Note: New Zealand and Australian figures are 2008 average

Using these proportions and overall IMS sales data, total RA related sales as well as current market shares of biologics in this indication can be estimated. In order to obtain sales data that are somewhat comparable across countries it is necessary to relate sales to the total population and if necessary correct for differences in prevalence.

Table 3-3 presents total sales and sales per 100,000 population for 2008 estimated in this way (not adjusted for any differences in price level or purchasing power). Sales per 100,000 population indicate substantially lower use in New Zealand than in Australia. Compared to the UK, where sales were estimated at around €600,000/100,000 population[2], sales in both New Zealand and Australia were low.

Table 3-3: Total RA related sales (€) 2008

	New Zealand	Australia
Total sales	5,066,519	82,307,912
per 100,000 population	121,074	397,663

3.3.2 Uptake of treatments

IMS reports total sales as sales at the list price without taking into account discounts, as official data on such discounts are not available in any country. Thus, actual sales (in Euro) in a number of countries could be lower than what is reported. Whilst it is not possible to take this into consideration for New Zealand the impact of this may be considerable, as substantial discounts are provided to the national drug funding agency PHARMAC. However, this only affects our estimates of the average sales per prevalent patient, and not the calculation of the proportion of patients treated as the latter is based on mg sold and thus is unaffected by any rebates.

For both calculations, full treatment years were assumed. 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 are even being treated intermittently.

Results are presented as uptake curves for the years in which data is available using both the upper and lower prevalence estimates. New Zealand is compared to Australia, the UK and E13[2], which is an average of the western European markets (Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland and the UK).

The curves can be interpreted as follows:

- The proportion of patients on treatment provides, in our view, the best comparison between countries, although they are influenced by the prevalence estimates that are used in the analysis. Both the individual country results, as well as the comparison between countries, would be inaccurate if prevalence in one or the other country were very different from the estimates used.
- The curves of estimated sales per patient add the price dimension to the proportion of patients on treatment. For instance, although the proportion of patients on treatment is lower in Australia than in the UK, the higher manufacturer prices in Australia lead to higher sales per patient than in the UK.

Overall, the results of this analysis show very low usage of biologics in the indication of RA in New Zealand, far lower than any of the Western European countries included in the E13 summary figures. This is further emphasized if one considers the fact that most countries included in the E13 group are well above the average E13, with only Germany, the UK, Italy and Austria below. The E13 average is thus essentially driven downwards by the low usage in 3 large countries (Germany, the UK, Italy) that represent large patient populations. Despite this, an estimated 11% of prevalent patients are on treatment in E13 countries. Figure 3-1 illustrates this, together with showing comparison to all European countries.

With the case of Australia, it is also possible to illustrate the impact of the prevalence estimates: if the same prevalence as for the UK is used (upper European prevalence estimate), Australia treats proportionally fewer patients than the UK. When using the lower prevalence rates, Australia uses biologics in a higher proportion of patients. (For sales per patient, Australia is higher in both cases, due to the devaluation of the British currency and thus a higher price in Euro in Australia).

Figure 3-1: Proportion of patients on treatment in New Zealand and Australia, compared to European countries

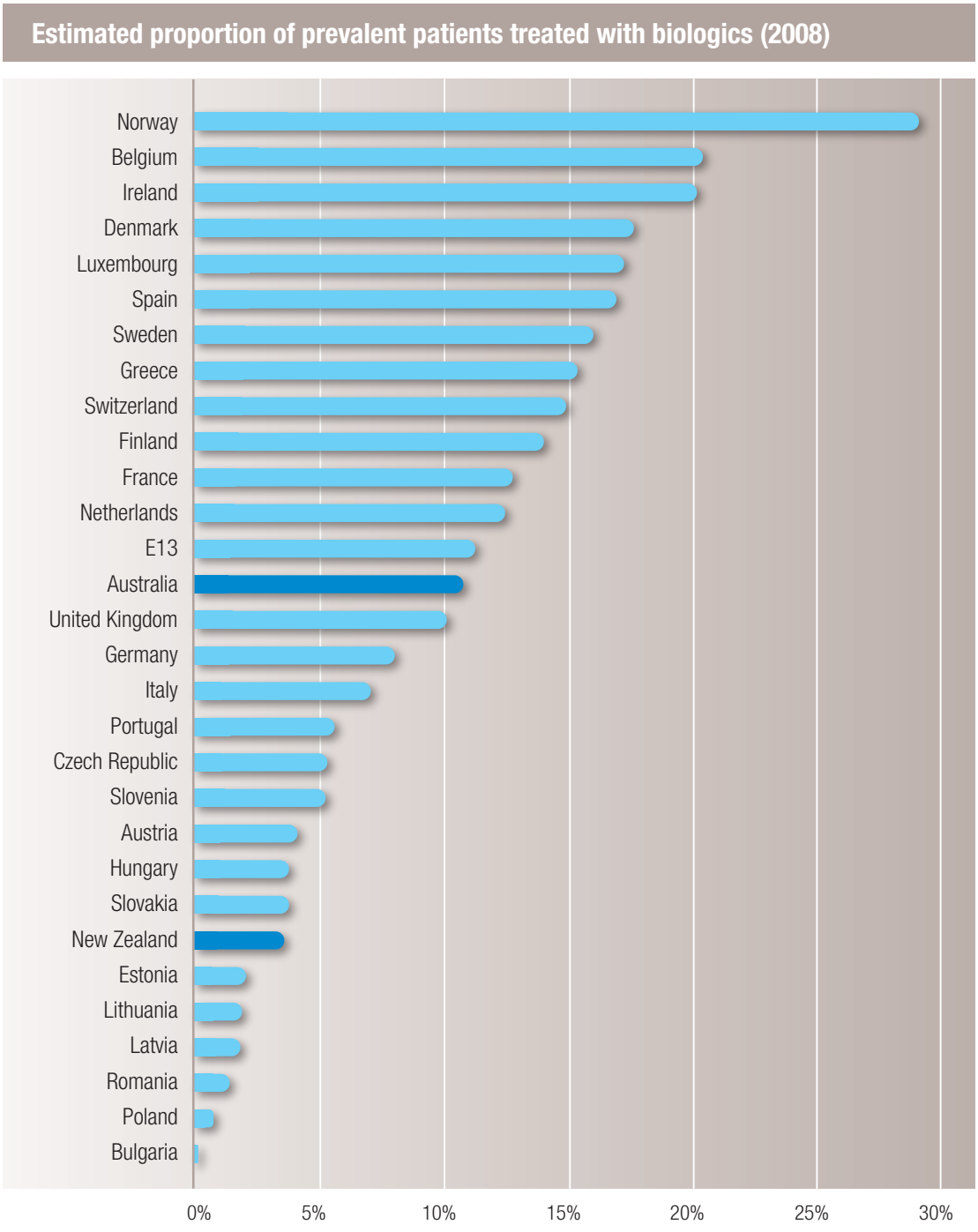


Figure 3-2: Proportion of prevalent RA patients treated, upper prevalence estimate

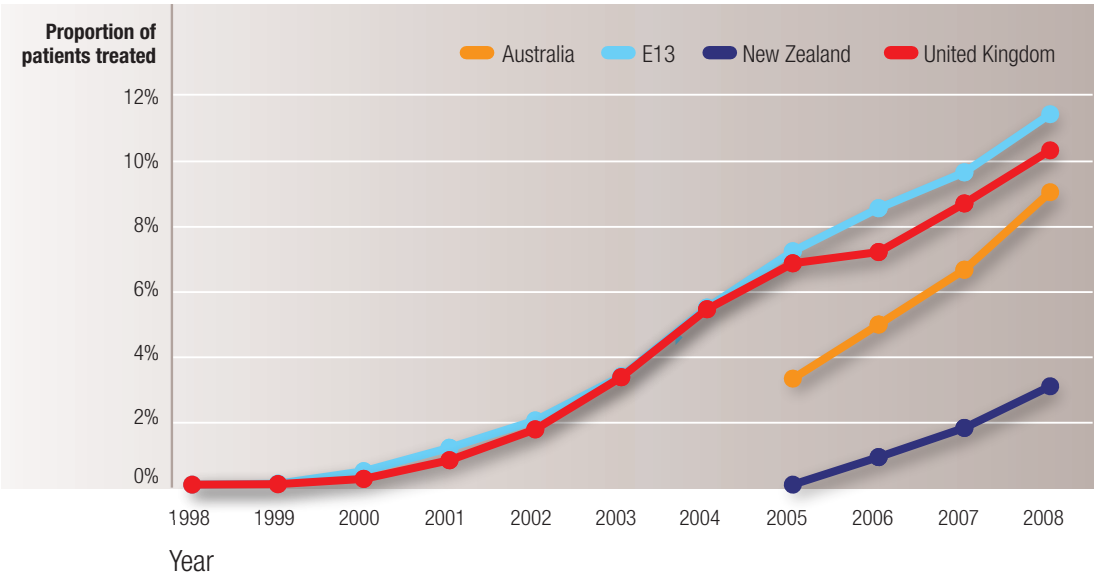


Figure 3-3: Proportion of prevalent RA patients treated, lower prevalence estimate

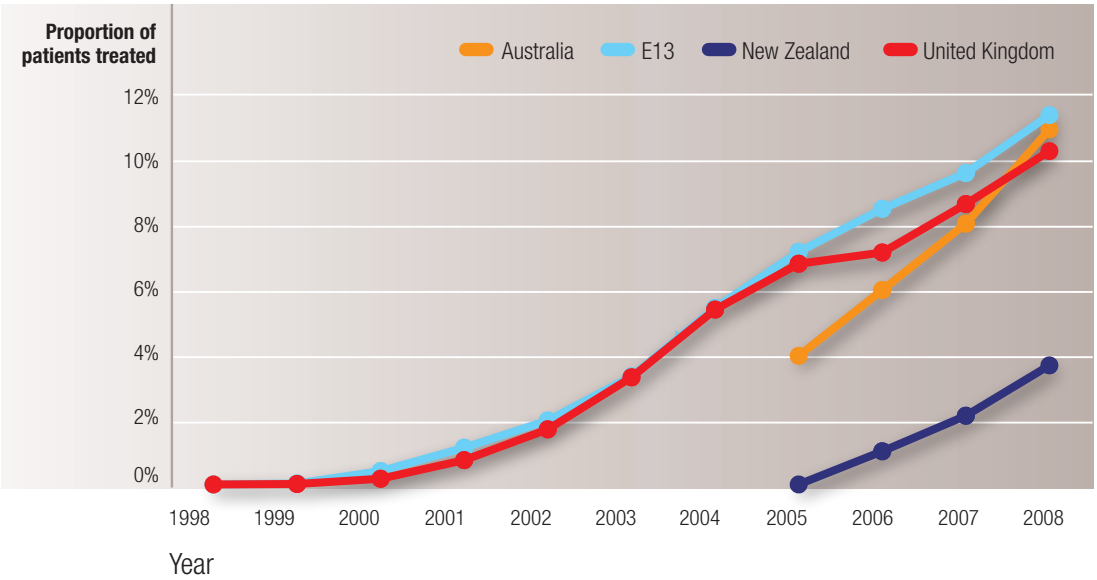


Figure 3-4: Annual sales (€) per RA patient, upper prevalence estimate

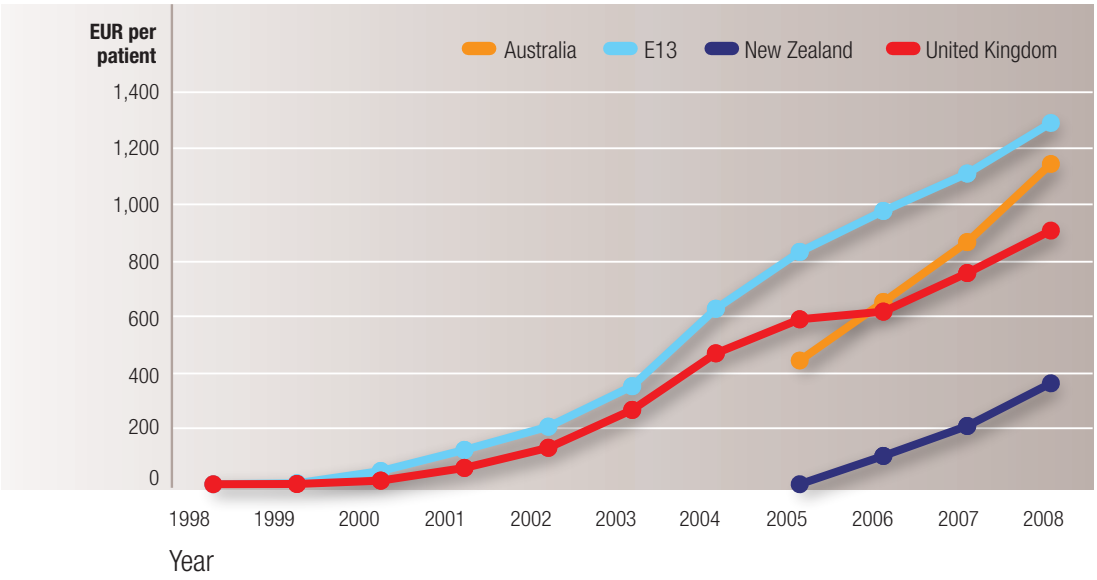


Figure 3-5: Annual sales (€) per RA patient, lower prevalence estimate

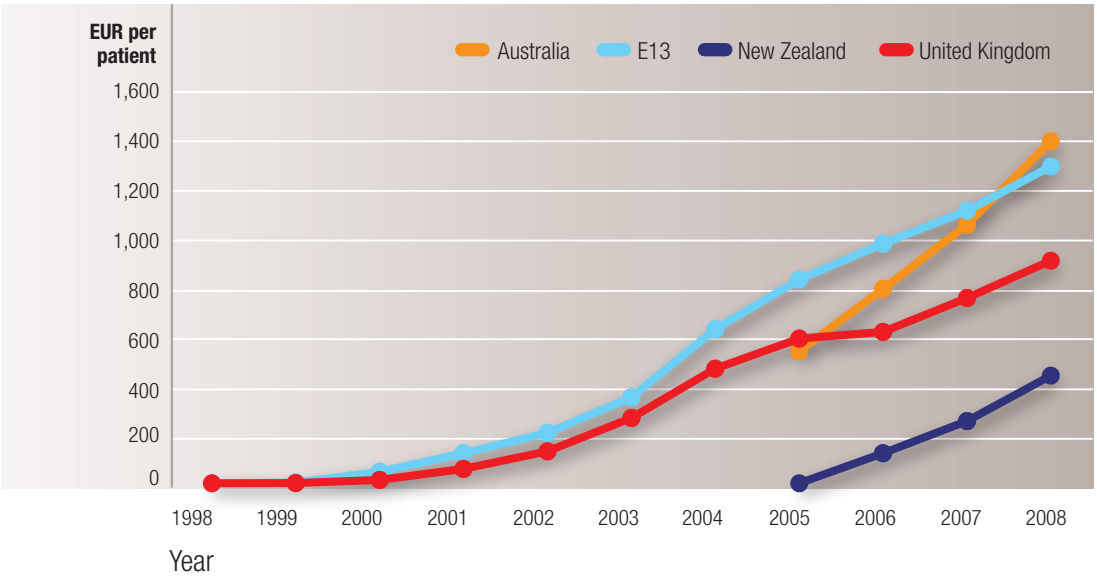


Figure 3-6: Proportion of prevalent RA patients treated with etanercept, upper prevalence estimate

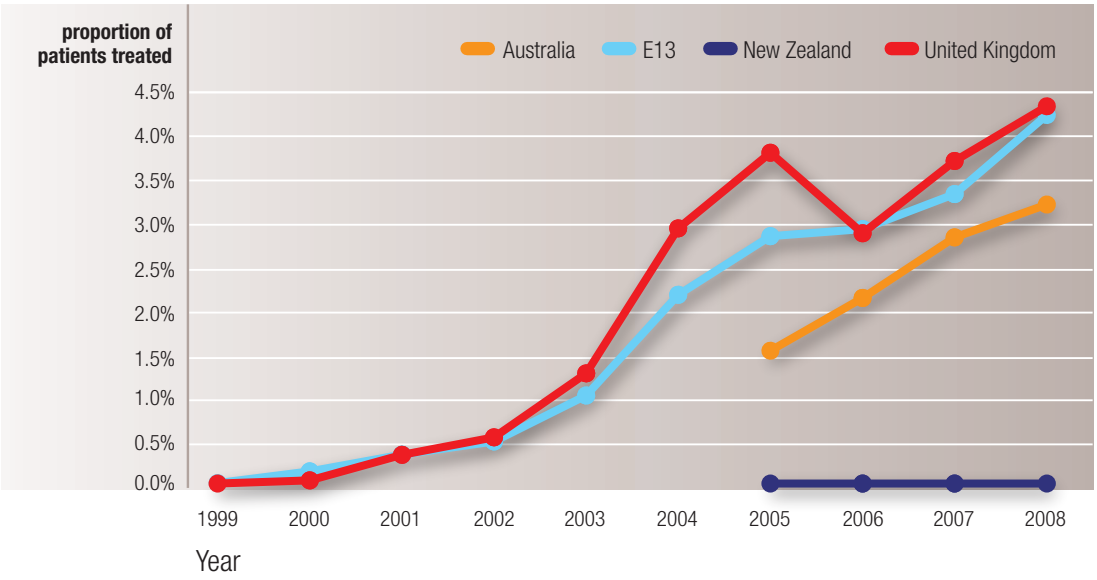


Figure 3-7: Proportion of prevalent RA patients treated with etanercept, lower prevalence estimate

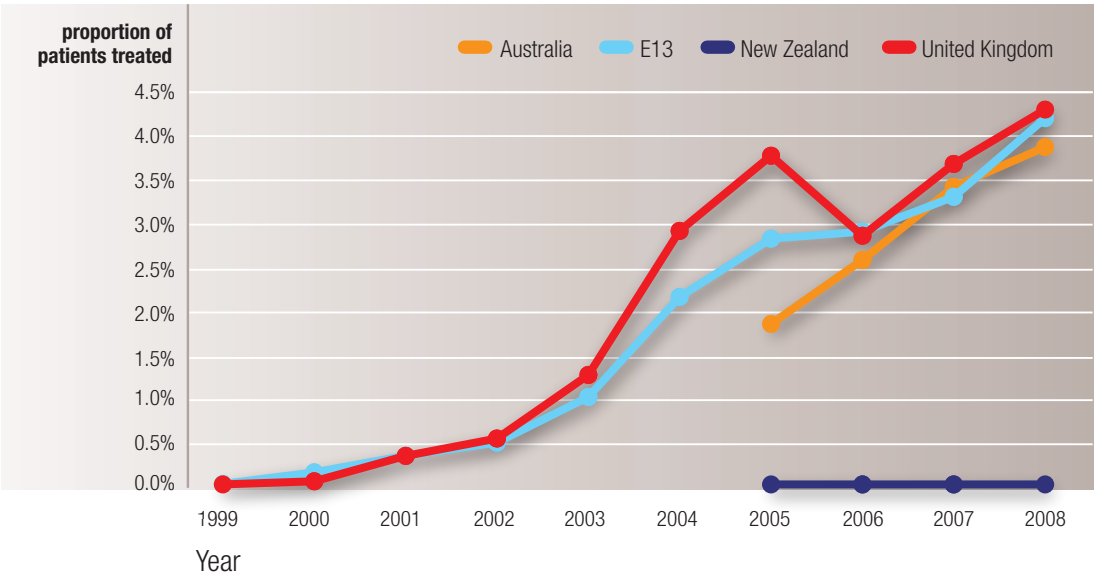


Figure 3-8: Proportion of prevalent RA patients treated with adalimumab, upper prevalence estimate

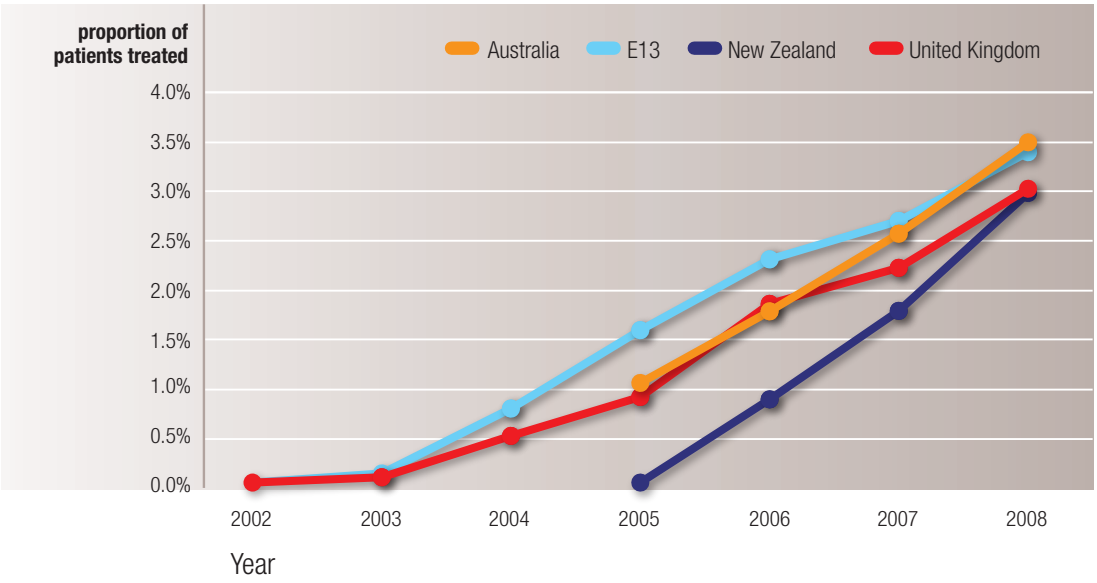


Figure 3-9: Proportion of prevalent RA patients treated with adalimumab, lower prevalence estimate

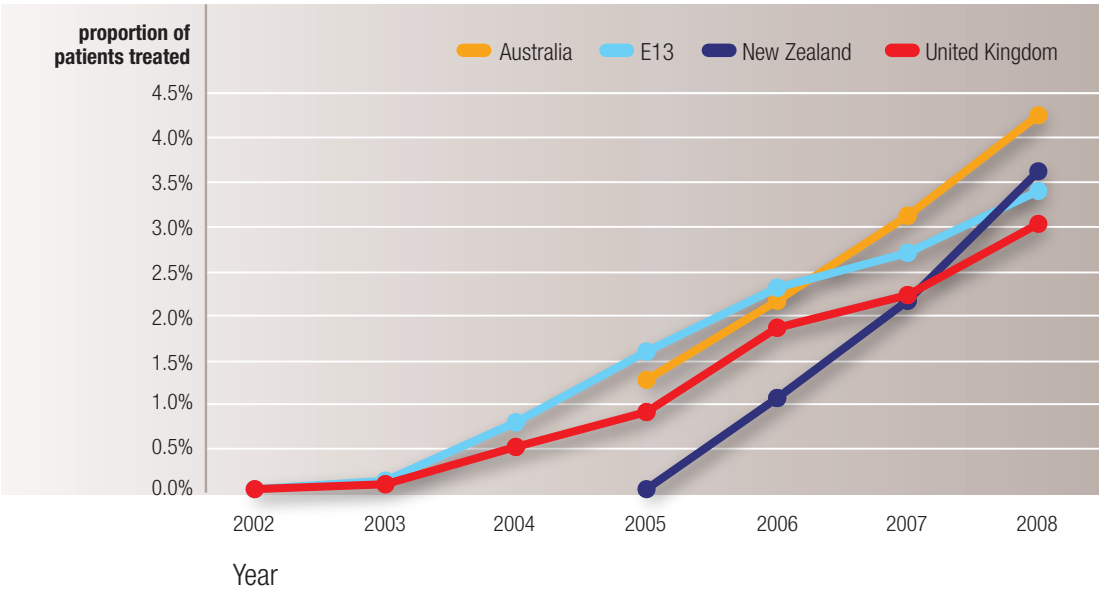


Figure 3-10: Proportion of prevalent RA patients treated with infliximab, upper prevalence estimate

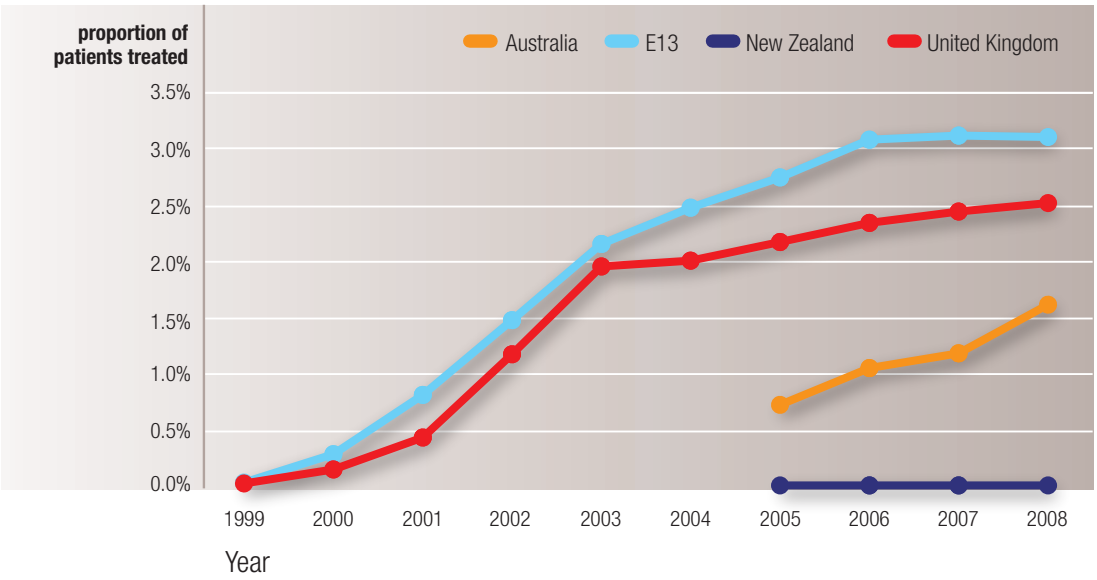


Figure 3-11: Proportion of prevalent RA patients treated with infliximab, lower prevalence estimate

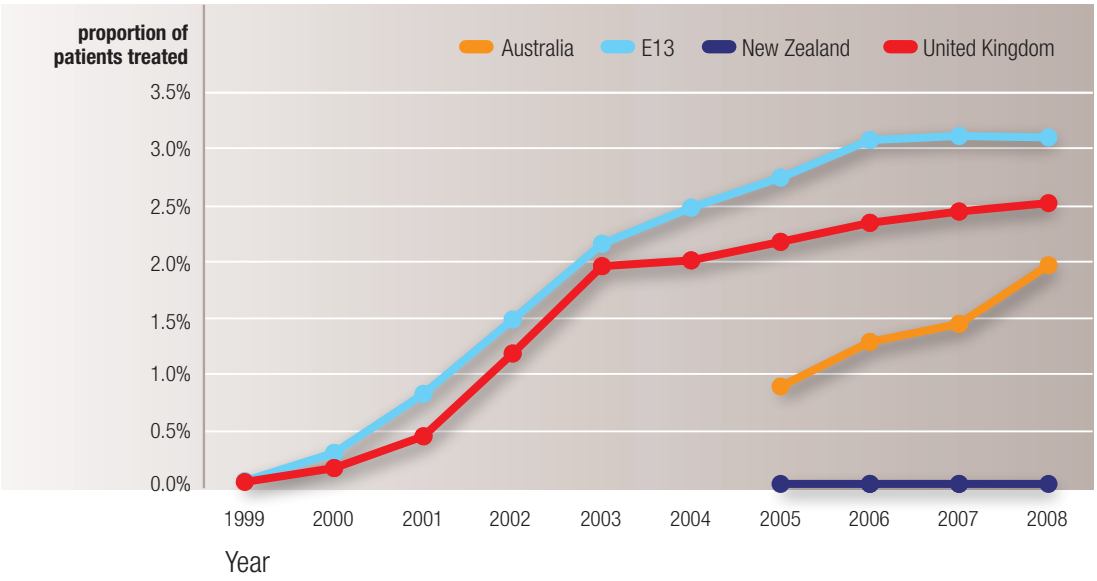


Figure 3-12: Proportion of prevalent RA patients treated with rituximab, upper prevalence estimate

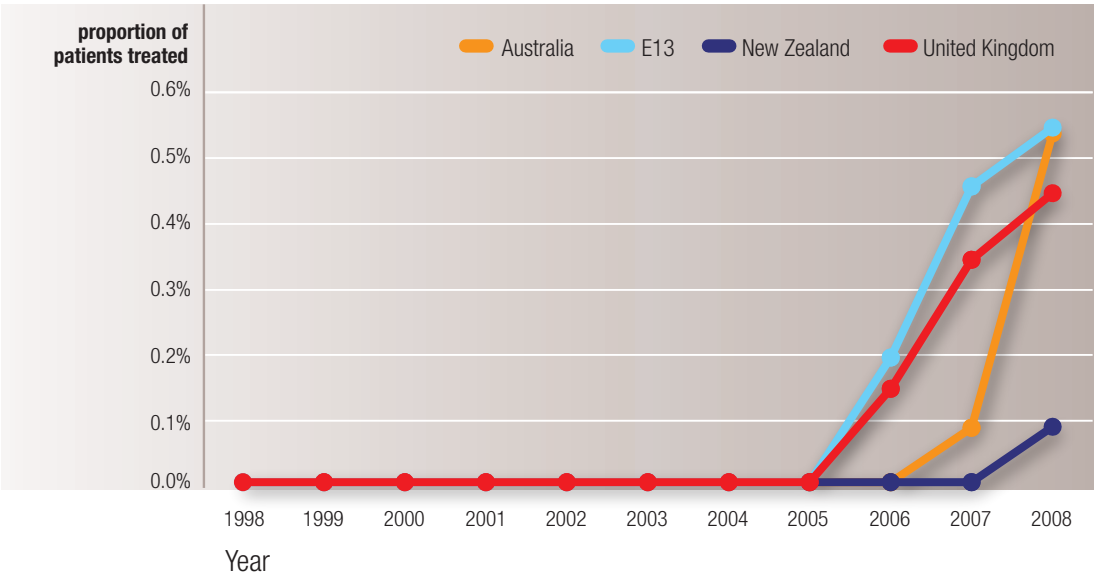
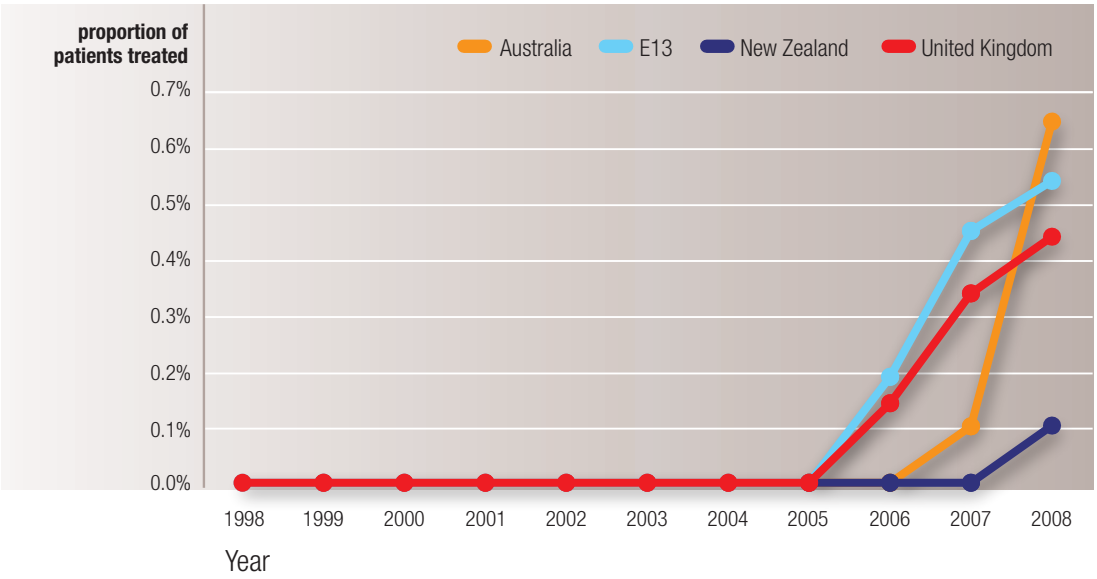


Figure 3-13: Proportion of prevalent RA patients treated with rituximab, lower prevalence estimate



3.4 Conclusion

To assess the uptake of biological treatments, information from different data sources were combined. Sales information on volume and value were obtained from IMS. Proportional sales in the indication of RA for the different drugs were based on best estimates only. Prevalence estimates were those calculated in Chapter 1.

As with most data sets, IMS data have some short-comings. In some countries, not all sales are captured, or influenced by the selection of panels of data providing organizations. This can lead to both under- and over-reporting. Also, sales values are calculated using the official list prices, thus excluding discounts that are given in a number of countries and to a number of payers. These represent however in general confidential information and are unavailable. In the case of New Zealand, discounts are likely to play a bigger role than in Europe, and therefore our estimates of sales per prevalent patient may be overestimated. (This can obviously easily be corrected by simply reducing the results by the assumed discount given on the one product that is used). It is important to remember, however, that this does not affect the main results, i.e. the calculations of the number of patients treated, as these were based on volumes rather than value.

Overall, the results of this analysis show a very low usage of biologics in the indication of RA in New Zealand, far lower than in any of the Western European countries included in the E13 summary figures. Usage is also substantially lower than in Australia, where usage at least approaches that of the UK. One should, however, not forget that the UK is one of the most conservative users amongst the E13 countries.

3.5 References

1. The economic cost of arthritis in New Zealand. *Access economics Pty Limited for Arthritis New Zealand www.accesseconomics.com.au* 2005.
2. Kobelt G., Kasteng F. Access to innovative treatments in Rheumatoid Arthritis in Europe. *www.comparatorreports.se* 2009.

Chapter 4 – Determinants of access to treatment

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4 Determinants of access to treatment

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 relationship between Gross Domestic Product (GDP), expenditures on health and global drug prices leads to a large difference in affordability between different states. In this study, New Zealand was found to have more difficulties to afford biological treatments than Australia or the UK, as price levels of biologics are similar but health care spending per capita is lower.

Health technology assessment studies (HTAs) and economic evaluations are highly relevant in the context of affordability. A treatment at a price between €10-15,000 annually 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. Whilst a considerable number of HTA evaluations and peer reviewed publications are available in Europe, very few were identified for New Zealand and Australia.

While there appears to be no doubt concerning the clinical effectiveness of biologics, different countries have had different views on how cost-effective they are. Although several have found biological treatments to be cost-effective, the reimbursement agency in New Zealand, PHARMAC, have found TNF inhibitors not to be good value for money, leading to the most restrictive reimbursement of the countries compared, with only one product covered. As estimated in Chapter 3, 3% of RA patients receive biological treatment in New Zealand. If we accept that around 20% of RA patients are eligible for treatment with biologics, a mere 15% of these patients have access to them, which is far below Australia and the UK at a level of coverage of approximately 45-50%.

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. Of the countries included in this report, New Zealand had the most restrictive guidelines for biological treatment and also the highest number of RA patients per rheumatologist, although these estimates were surrounded with some uncertainty. Lack of rheumatologists or lengthy referral processes to specialists can lead to long waiting times for consultations and hence late diagnosis and treatment.

No one of these factors in isolation explains the differences in uptake of biologics between countries. Differences between countries with similar economic conditions are explained by a combination of economic organizational 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 system for drugs, this means that inclusion in the 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 fulfill before a new drug achieves government funding, alongside clinical safety, efficacy, effectiveness and quality that are requirements for marketing approval by national regulatory 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.

The differences in proportion of patients receiving biologic treatment in different countries is explained by several factors, including differences in wealth (GDP) especially in regions where drugs are priced in a narrow range to avoid parallel trade, reimbursement processes, access to specialists, medical practice and treatment guidelines.

4.3 Affordability

To evaluate the possibilities in different countries to incorporate the biologic drugs into the health care budget, the European report had established an "affordability index" for each country. Indices for relative prices and relative expenditure per capita were first established, using Germany as an index of 100 in both cases. Comparing the two indices provides an indication on how well biologics at the given price can be taken up within the health care budget. A higher affordability index indicates more difficulties to afford. For this report, New Zealand and Australia were added to these estimates.

Thus, prices of biologics, health expenditures and affordability in New Zealand and Australia were compared to all European countries, to put them into a larger perspective. Both Australia and New Zealand have relatively high prices of biologics compared to the UK (mostly due to the devaluation of the British currency versus the Euro), whereas with regards to health expenditure, New Zealand is on the lower end. This leads to a high affordability index for New Zealand (mainly driven by the lower health care spending), i.e. theoretically more restricted possibility to include these expenses in the health care budget. It should be noted that the prices of biologics are based on IMS data on volume and value of sales which may overestimate the actual costs as they do not include any rebates. This is expected to have minor effect on the comparative indices as this affects all countries. However, excluding rebates may have a more pronounced effect on the New Zealand estimates as rebates for adalimumab are unofficially reported to be substantial, at around 30-40%[I]. A lower price index for New Zealand would result in a lower affordability index, indicating better ability to include the drugs within the budgets. However, without accurate information on the rebates, the magnitude of this change cannot be calculated.

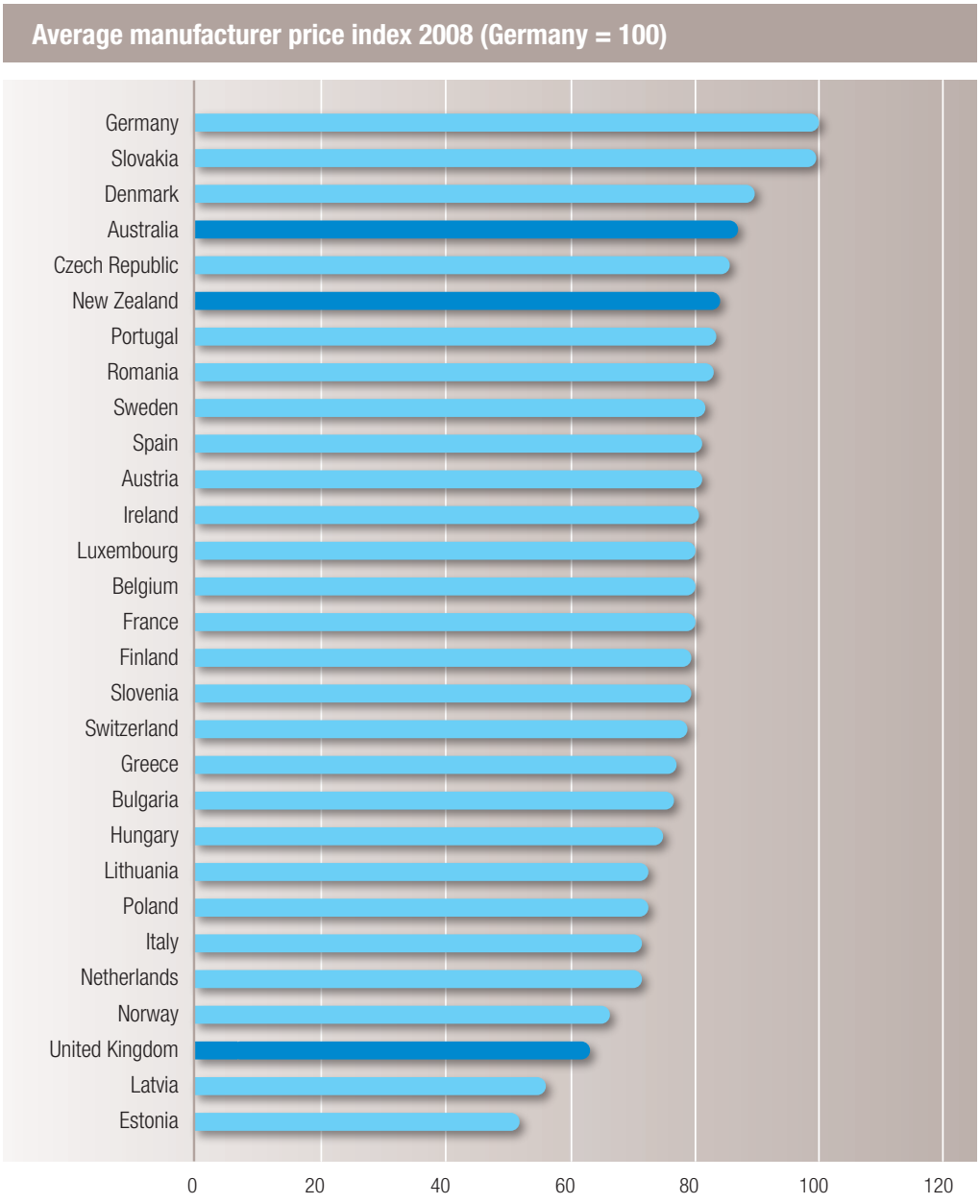
I PHARMAC "Memo to DHBs regarding biologic treatments for autoimmune disease - February 2009" (unpublished)

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

Country	TNF price index[i] Germany = 100	Relative health expenditure/capita[iv] Germany=100	Affordability index [vi]
Australia	**88**	**87**	**101**
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[ii]	31[v]	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[iii]	30[v]	190
Lithuania (uncorrected)	73	25	294
Luxembourg	81	116	70
Netherlands	72	94	77
New Zealand	**85**	**70**	**121**
Norway	67	134	50
Poland	73	27	271
Portugal (hospital)	84	63	133
Romania	84	19[v]	440
Slovakia	100	39	257
Slovenia	80	64[v]	126
Spain	82	73	113
Sweden	83	95	87
Switzerland	80	128	62
United Kingdom	**64**	**82**	**78**

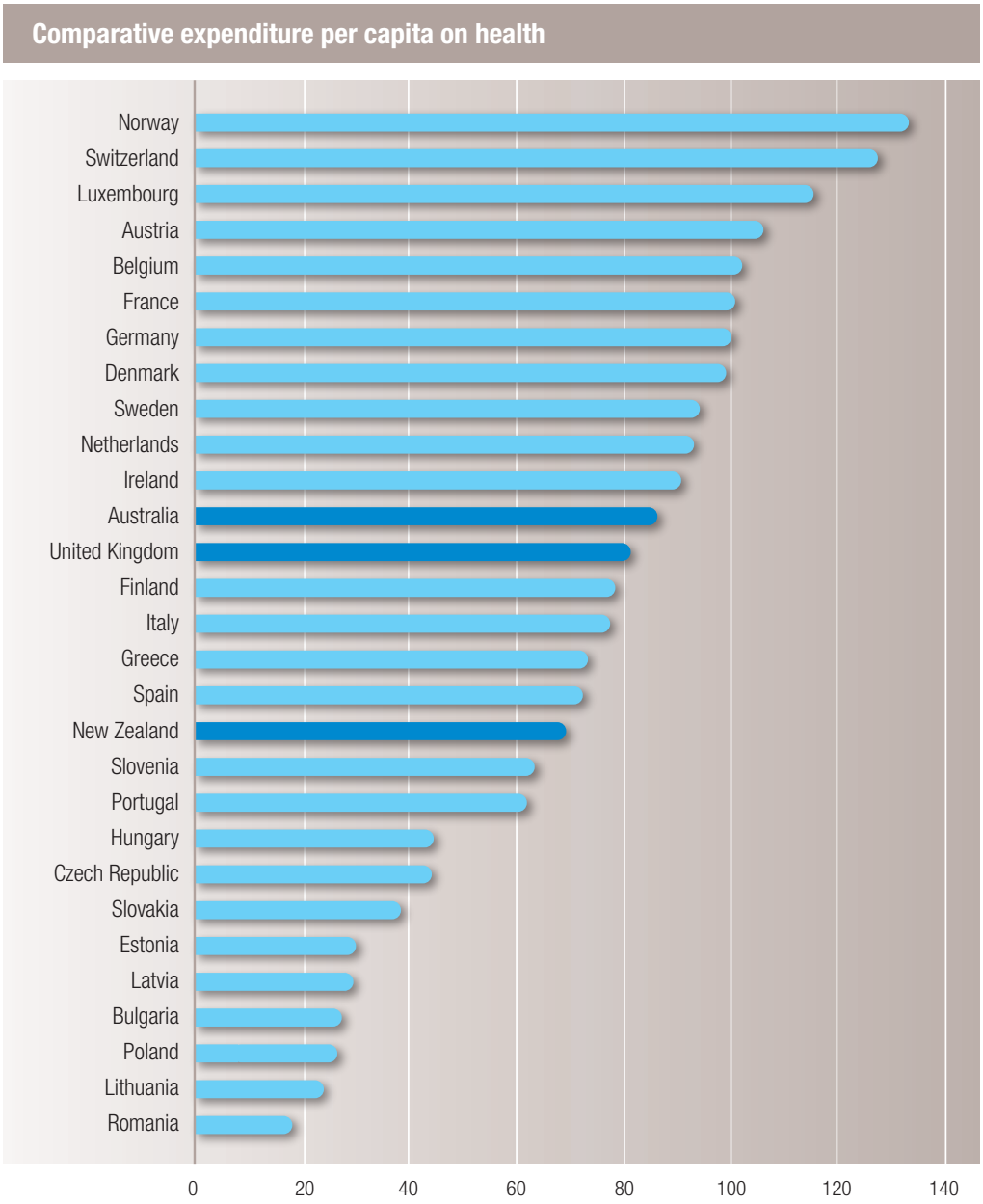
i Price index based on un-weighted average of the 3 TNF inhibitors Germany = 100
ii Data for only 1 product
iii Data for 2 products only
iv Source: OECD Health Data 2008
v Source: WHO statistical information system, 2006 adjusted
vi Calculated comparing the index of health care expenditures to the price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

Figure 4-1: Price comparison across countries (Germany=100)[i]



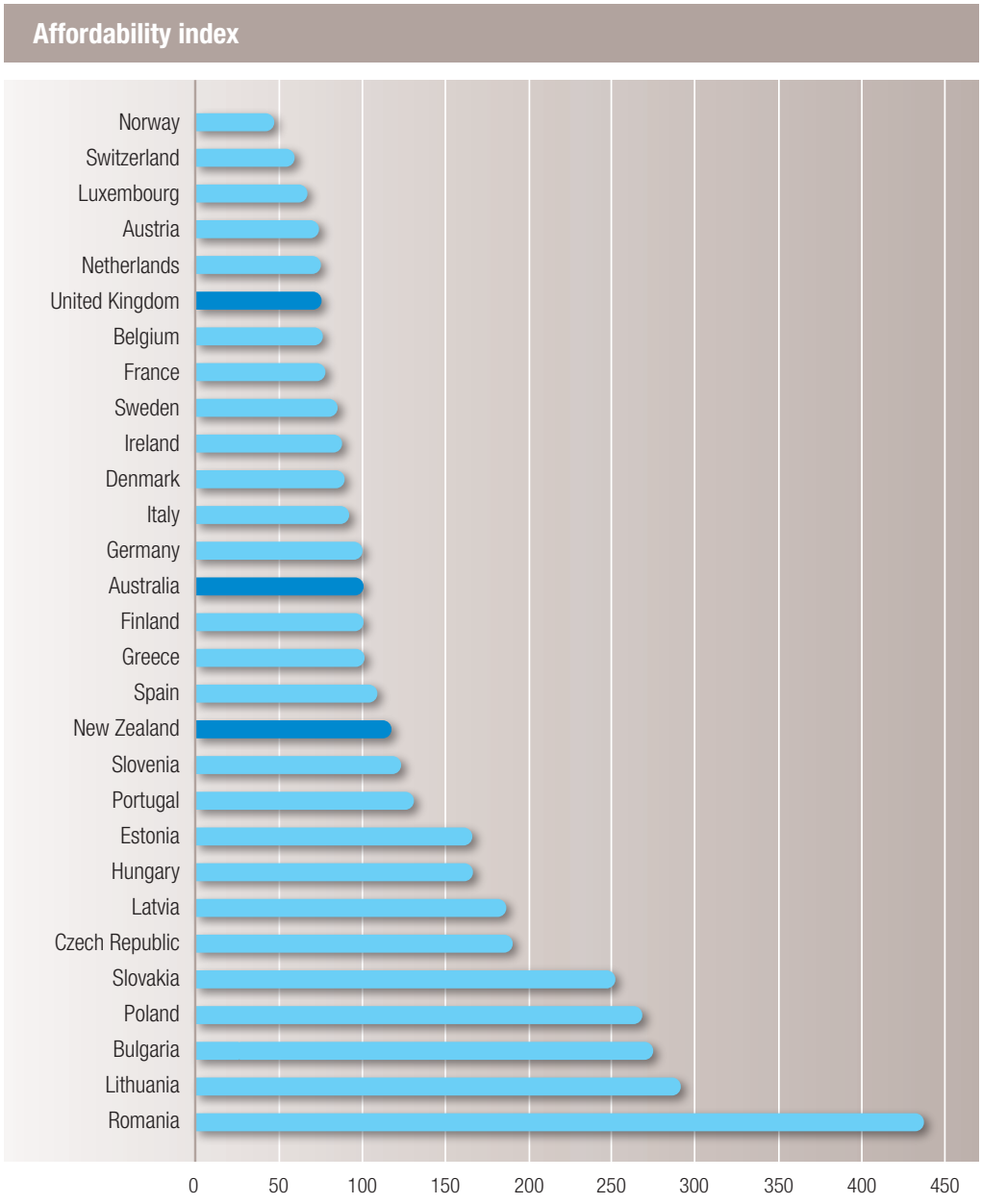
i TNF inhibitors only, index based on unweighted ex-factory prices
(Note: only infliximab available in Estonia and adalimumab in New Zealand)

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 were therefore likely influenced by initial caution regarding their adverse event profile. As studies have demonstrated the efficacy of early treatment with biologics[1-5] this may increase the proportion of eligible patients in the future. Payers may, however, be reluctant to fund biologics for larger patient populations.

If we accept that up to 20% of patients would be eligible for biologic treatment, this means that on average, about half of eligible patients actually receive treatments. The range within Europe is large, from close to 100% of eligible patients in Norway and Belgium to only around 50% in the UK, 25% in Germany and Italy and even less in Austria, with around 15%. New Zealand is well below the European average with 3% of the prevalent and hence only around 15% of patients on treatment. Australia fares slightly better, reaching almost the levels of treatments seen in the UK, with 9% of prevalent and 45% of eligible patients on treatment.

4.5 The reimbursement process

The time of the reimbursement process can vary, depending on the country and also on the technology in question. Both New Zealand and Australia have formal mechanisms for national reimbursement decisions, as in most European countries. In both countries, there is a formalized decision making process of reimbursement, where economic evaluation and the issue of cost-effectiveness play important roles. This is similar to European countries such as Belgium, Finland, the Netherlands, Norway, Portugal and Sweden. In the UK, on the other hand, no specific decisions have to be made before a drug can be prescribed on the national health service. Although no formal process for pricing and reimbursement of drugs exists, the government can still indirectly exert a control via price cuts and paybacks from companies under the system of profit control.

Within a reimbursement process it is sometimes possible to define the eligible patient populations more restrictively than in the market access authorisation by the regulatory agencies. This is most apparent in New Zealand where only adalimumab is reimbursed for RA by PHARMAC, although other biologics have gained approval for market access by the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) for the indication of RA. In contrast, all registered biologics for the treatment of RA, with the exception of the recently approved biologics, are listed in the Pharmaceutical Benefits Scheme (PBS) in Australia and are thereby covered by the reimbursement system.

In New Zealand, reimbursed community and cancer medicines are listed in the PHARMAC schedule. Adoption of newer and more expensive products is generally low and slow, and if adopted, they tend to be listed under the PHARMAC special authority system. In this case, to gain reimbursement, a prescriber must request government subsidy for a particular person through filling out a special authority form. For adalimumab (the only biologic reimbursed for RA), this must be done by a rheumatologist and is valid for six months after approval[J]. This administrative hurdle may further limit timely access to treatments for RA patients, implicating that the delay before initiating biological treatment is likely to be longer in New Zealand compared to other countries.

A further hurdle in accessing RA treatments in New Zealand is the fact that, outside of cancer treatments, PHARMAC are not responsible for decisions to reimburse medicines which are hospital administered. Decisions to reimburse non-cancer hospital administered treatments reside with each of the 21 District Health Boards (DHBs). DHBs have variable and limited capacity and capability to assess, prioritise and manage which hospital pharmaceuticals are clinically and cost effective and should therefore be funded for their populations. This creates large differences in the service mix, i.e. medicines availability, at different DHBs and significant "postcode access" to hospital prescribed medicines, especially those which have a high acquisition cost such as the biologic treatments for RA.

4.6 Treatment guidelines

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

J http://www.pharmac.govt.nz/2010/04/01/SAForms.pdf (Last accessed 29th March 2010).

Many countries have issued clinical guidelines for the treatment of biologics in RA to foster use of these therapies, appropriate both from a medical and economic point of view. As in the UK, the guidelines can also define a sequence in which the biologics should be used. In New Zealand, there are no official guidelines, but the PHARMAC special authorisation form for adalimumab is in practice used as treatment guidelines. In Australia, the Australian Rheumatology Association has drafted guidelines for treatment with biologics[6].

The definitions of eligible patients in guidelines can be expected to heavily influence the access to treatment in the different countries. Criteria used in the three countries compared in this report are listed in Table 4-2 below and relates them to usage estimated in our study. The New Zealand guidelines do not explicitly state in which time the effect of treatment should be evaluated, but as the special authority form needs to be renewed every six months, this may in practice be the time frame for evaluation.

Table 4-2: Eligibility criteria for access to biologics and related use

Country	Level DAS28 required	Previous DMARD treatment required	Minimum time on previous DMARDs	Evaluation of effect	Estimated use of biologics
New Zealand	Severe and active erosive RA >6 months	4, one of them MTX	3-9 months	None stated	3%
Australia	>3.2	2, one of them MTX	3-6 months	3-4 months	9%
United Kingdom	>5.1	2, 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. Apart from the macroeconomic conditions, prices have a poor explanatory value for differences in uptake between the countries. Indeed, ex factory prices in the countries investigated in this report 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. Companies also provide confidential rebates of their products, which will have an impact on the actual final cost. The magnitude of this rebate to the total cost will depend on the system, i.e. if the prices are negotiated at hospital level or at national level (as in New Zealand). We have therefore used manufacturing prices for the comparisons presented in the previous chapter.

High prices may partly explain overall restraints in usage due to poor affordability, but organisational issues in health care financing, such as budgets, are better explanations of the differences than prices. The price comparison used in the calculation of the affordability index in the previous chapter may also have been "disturbed" by recent currency shifts versus the Euro, which should be taken into consideration when interpreting the results (e.g. explaining the relatively low price in the UK). The effect of these currency changes will be an increase in parallel export, still only expecting to have minor influence on the usage of biologics.

4.8 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. HTA has been defined 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[K]. Economic evaluations are thus an integral part of HTA and reports include a review of previously published economic evaluations for the treatments in question 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 and 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 the fact that economic evaluations are country specific, guidance documents issued by NICE appear to have an impact on decision-makers beyond the borders of the UK.

Agencies currently conducting HTAs in New Zealand and Australia include PHARMAC and The Health Services Assessment Collaboration (HSAC) in New Zealand and Adelaide Health Technology Assessment and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia. However, only few HTAs were publicly available and/or investigated treatments for RA.

- An HTA in Australia for RA investigated the use of MRI in diagnosis of RA[7], but as the technology falls outside the scope of this study, it was not investigated any further.
- A report evaluating hospital products by PHARMAC in New Zealand[L] has referenced a PHARMAC HTA and concluded that the TNF inhibitors for the treatment of RA were not good value for money at current prices, when compared to methotrexate. The results yielded a cost per QALY gained of NZD191,000 (approximately €90,000)[8], falling in the upper end of other cost-effectiveness analyses of treatments with TNF inhibitors.

In Europe, there are several technology assessment reports of the new biological RA drugs available, but most are from NICE and concern the two TNF inhibitors that were first introduced (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 the basis for the NICE treatment guidelines[9]. This first report assessed the cost per QALY gained with etanercept 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[10] 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[11]. The report concluded that TNF inhibitors are most cost-effective when used as last active therapy, £24,000-38,000 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[12].
- In 2007, NICE published guidelines on rituximab in the treatment of RA[13]. Rituximab in combination with methotrexate was recommended as second line biologic after failure of at least one TNF inhibitor therapy. The decision was based on clinical and cost-effectiveness data submitted by the manufacturer as well as the registration of rituximab as a second line biologic.

K http://www.eunethta.net

L The full HTA was not available an in the referenced report, no specification of methods was given and the HTA has not been updated since 2005.

- 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 RA[14].
- Finally, a guidance for abatacept issued in 2008 (revision planned for 2010) did not recommend its use within the marketing authorisation; use was recommended only for patients currently on the drug[15]. The interpretation of this negative guidance is that compared to rituximab, which has the same market authorisation (patients failing on TNF inhibitors), the cost of abatacept is higher, thus rituximab is the preferred second line biologic treatment after a first TNF inhibitor.

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 their cost-effectiveness is currently less clear.

4.9 Health economic studies in RA

In the European report, a literature search was conducted and the main results from it are presented below. No cost-effectiveness analyses apart from what has already been presented in the previous section of biological treatments valid for the Australian and New Zealand setting were identified.

There has been an increase in health economic studies in RA since the late 1980s, with peaks of published studies around the time of launch of a new treatment. RA modeling has a long tradition, but has changed over time from modeling short term effects (6 month trial) to modeling the long term outcomes for cost-effectiveness, as is now standard practice in a chronic disease such as RA[16]. Models should represent best available knowledge, and hence, are only as good as the underlying data. Regardless of the modeling 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 which are then subject to different opinions, interpretations and critiques.

Published studies of biological treatments have shown quite diverse results, as shown in Table 4-3. Key differences in published studies 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).

At the first introduction of biologics, the question examined has been whether the new treatment was cost-effective compared to older treatments, and for which patients. 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 Sweden (ARTIS, and sub registries SSATG and STURE). A recent analysis using 10-year data from the SSATG sub-registry found that earlier introduction of biologic treatments led to lower costs and higher utilities over 10 years than starting late[17].

Registries have been established in Europe as well as in New Zealand[M] and Australia, 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 datasets better information on disease progression on treatment could be gained. Registry data can provide an opportunity to estimate the effects of biological treatments in clinical practice and the effect the treatment has had on costs and quality of life.

M The New Zealand RA registry was started in 2006 and ended two years later, providing follow-up data of two years.

Table 4-3: Published cost-effectiveness analyses of biological treatments

Country	Perspective	Interventions compared	Data source	Patients included (baseline HAQ)	Time-horizon	Result	Currency and year	Ref
Finland	Healthcare provider	INF / other standard care		Early disease (1.3)	Mean 21 months	€52,000	€ 2007	18
Netherlands	Societal	Monotherapy / comb / comb+pred. /comb+INF	Investigator trial	Early disease (1.4)	2 years	IFN vs. next best alt: ICER €130,000	€ 2008	19
Sweden	Societal	INF+MTX / MTX	Clinical trial	Advanced active RA (HAQ 1.8)	10 years	16,100€/ QALY	€ 2002	20
Sweden	Societal	INF and ETA / compared to baseline	Registry	Advanced RA (HAQ 1.5)	1 year	43,400€/ QALY	€ 2003	21
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	RIT 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 Societal	INF+MTX / MTX	Clinical trial	Advanced active RA (HAQ 1.8)	10 years	34,800 £/ QALY 29,900 £/ QALY	GB£ 2002	20
UK	NHS/PSS	ETA, INF, ADA / DMARD sequence	Registry	Advanced active RA (HAQ 2.1)	Lifetime	23,900 £/ QALY	GB£ 2006	29
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	GB£ 2004	30

ADA = adalimumab, ETA = etanercept, INF = infliximab, MTX = methotrexate, RIT = rituximab
DMARD = disease modifying arthritic drugs, NHS = National Health Service, PSS = Personal Social Service

4.10 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. The European report indicated that the shortest possible time to prescription, in most countries, was 6-12 months, whereas given the limited reimbursement, administrative hurdles and initiation of biological treatment later in the course of the disease according to guidelines, the time may be even longer in New Zealand. Also, a delay in initiating biological treatment of 2-3 years is common because of delays in seeking care, diagnosis uncertainty, waiting for lab results, referral process, failing of conventional DMARDs etc.

In Europe, the rheumatology community has made large efforts to promote early diagnosis and early treatment and studies have indicated that the time to diagnosis and treatment has decreased over time. Still, treatment within 6 months is 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 or where there is a lack of specialists leading to long waiting times prior to consultation, treatment within 6 months is seldom achieved.

Table 4-4 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 orthopedics are also treating patients with RA. Additionally, in the UK, specialist nurses are heavily involved in routine follow-up of RA patients, which are not included. The number of rheumatologists for New Zealand was the number of full time equivalent rheumatologists, possibly resulting in a lower overall number. Nevertheless, the figure gives an indication of the differences among countries in terms of the density of rheumatologists.

Table 4-4: Number of RA patients per rheumatologist

	RA patients/rheumatologist
New Zealand[i]	986
Australia[ii]	333
UK[iii]	236

Sources: [i]Harrison 2004[31]; [ii]Workforce participation[32]; [iii]Eurostat Note: high prevalence rates were used for New Zealand and Australia.

New Zealand had the lowest uptake of biologics in this comparison as well as the highest number of patients per rheumatologist, although the limited uptake of biologics probably is better explained by the limited reimbursement. The number of patients per rheumatologist in New Zealand is higher than in any of the reported European countries, although the number of rheumatologists may be slightly underestimated.

Finally, only two of the established biologics can be self-injected (etanercept and adalimumab), while the third (infliximab), as well as the newer agents launched (rituximab and abatacept) or about to be introduced (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. The burden on the health care system will differ between the therapies requiring infusion as they require diverse treatment intervals, which should be accounted for when assessing their burden on the health care system. It is however impossible to make a general assessment of this, as it is hospital specific rather than a regional or national issue.

4.11 Conclusion

There is no one explanation for the differences in up-take of the biologics in the different countries of this comparison. A number of factors play a role, including level of health care spending, prices of treatment, restrictive treatment guidelines, budget restrictions, administrative hurdles and access to specialists.

Although prices of biologics were on similar levels in countries included in the comparison, the results suggest that New Zealand may have more difficulties incorporating these treatments into the health care budget, as health care spending is at a comparatively low level. However, the low level of uptake of biologics for RA in New Zealand cannot solely be explained by these macroeconomic factors. Rather, New Zealand appears as the country with the most restrictive reimbursement for biologics, including administrative hurdles for reimbursement. Additionally, treatment guidelines stipulate a start of biological treatment later in the course of the disease with no clear evaluation strategy in New Zealand compared to the other two countries. This, plus the high number of patients per rheumatologist, may to a large extent explain that New Zealand has the lowest uptake of biologics among all Western European countries as well as Australia.

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Chapter 5 – The value of treatment

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5 The value of treatment

5.1 Summary

This chapter discusses current knowledge of the value of biologics, focusing on parameters that affect health economic results. Whilst a comprehensive review is beyond the scope of this chapter, 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 in halting or slowing the underlying joint destruction, and even improving 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 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 joint erosions, and have been used earlier and earlier in the disease process. Traditional small molecule DMARDs 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, three 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 of joint damage both in established and early RA, particularly in combination with methotrexate. The more recently approved agents, with different mechanisms of action, have shown a similar overall effectiveness, including in patients with an inadequate response or intolerance to a TNF inhibitor. In this latter group, early observational data indicate that effectiveness may be improved compared to switching to a second TNF-inhibitor[3]. (For a summary on clinical effects, see Smolen and Aletaha[1].)

5.3 Cost-effectiveness in clinical practice

Despite this uncontested clinical effect, the use of biologic agents is restricted in many ways, mainly due to their price. Partly this may be due to budgetary or affordability reasons, partly due to the fact that the value (what one obtains) is perceived not to be in line with the price (what one pays). However, the evidence of the value is not only built up with new trials, but also with data from clinical practice and registries. However, it is 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, modeling 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 TNF inhibitors were indeed treated, as shown in an early Swedish study[4]. 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 analyzed 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 7,083 patients treated with TNF inhibitors drugs and 870 controls treated with standard DMARDS from the same registry[5]. 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 TNF inhibitor group, and mean HAQ scores were 1.6 in the control group versus 2.1 in the TNF inhibitor group. Although modeling techniques allow adjusting for such a difference, the question remains whether the 870 patients in the comparator arm are truly comparable or whether they represent a group that either does not qualify, cannot tolerate, or has withdrawn from TNF inhibitors. Regardless, 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. (Modeling studies based on clinical trials are not included here but have been presented in Chapter 4.) 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

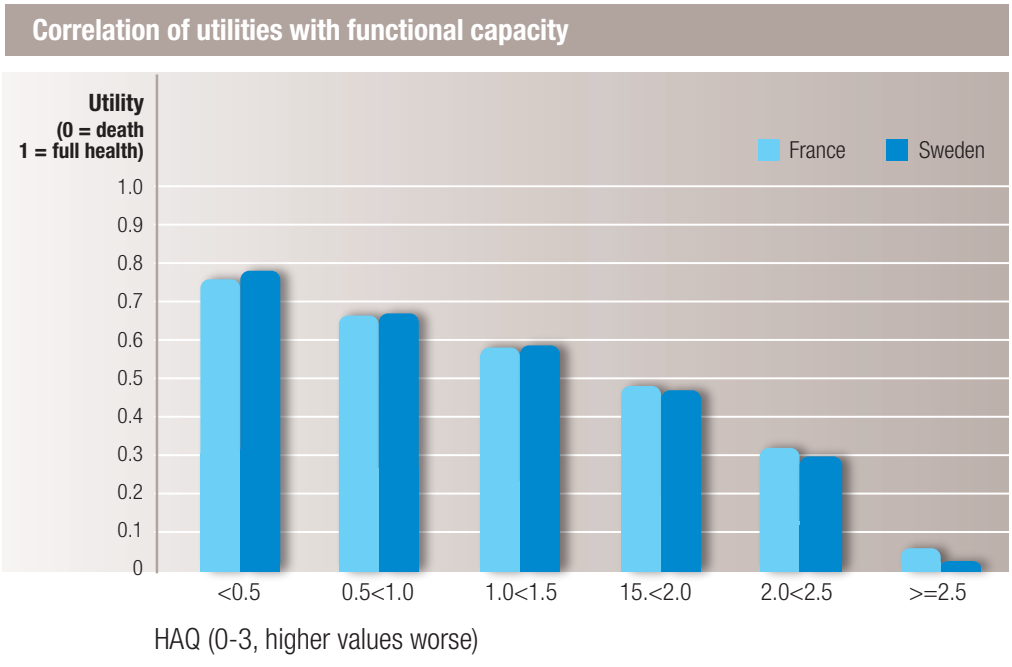
5.4.1 Effects on quality of life and utility

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. It is generally well accepted 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)[6-7]



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 done in the Norwegian RA registry, and results showed that between 1994 and 2004, overall health status of patients with RA improved[8] (Figure 5.2). The number of respondents between 20 and 79 years of age were 931; 1,025; 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)[8]

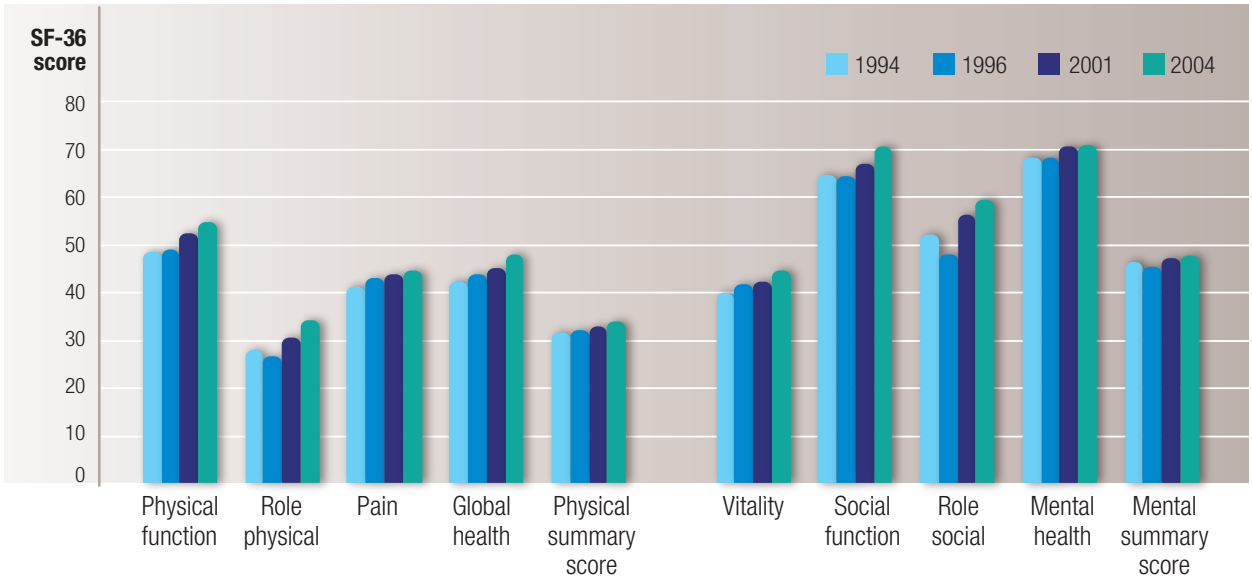
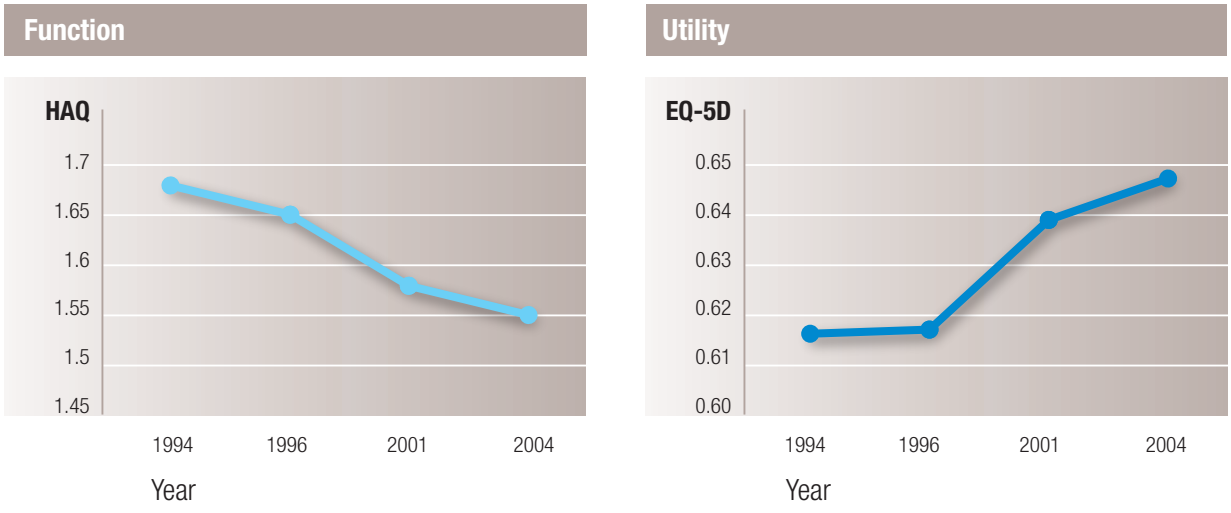


Figure 5-3: Change in function and utility over time (HAQ, EQ-5D)[8]



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 earlier 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[9]. Baseline disease activity for 1,813 patients recorded in the registry between 2000 and 2005 decreased from 5.9 to 5.3 (DAS28). Despite 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 persistance was around 70% in all years.

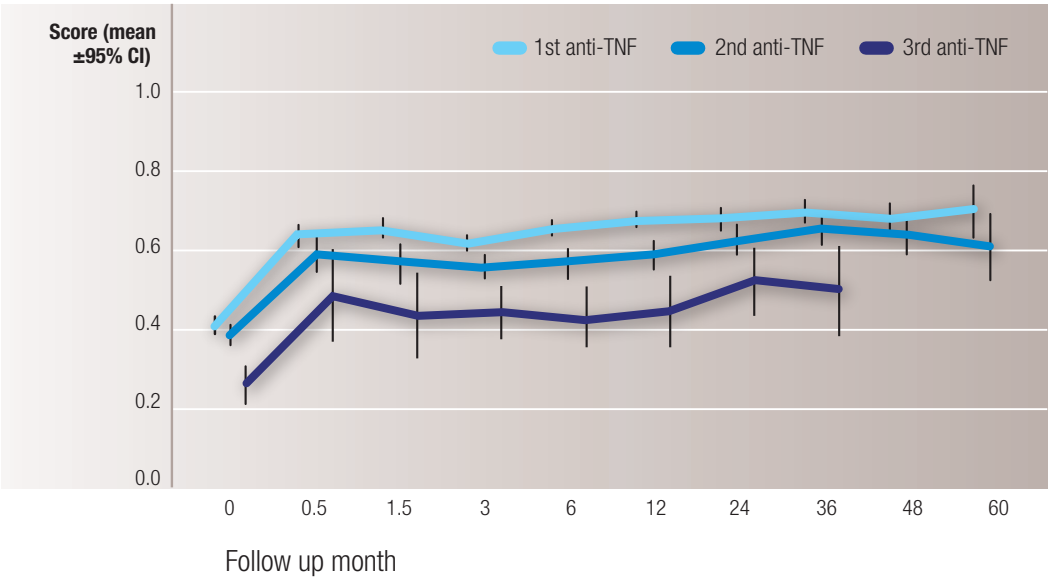
Thus, not only does overall better access and management improve patients' health status, more intensive management and earlier treatment with biologics also provides better response. This should logically lead to savings in costs other than the intervention costs. This has also been shown in a Scottish study (TICORA) where patients were randomized to intensive and standard management10 (see Chapter 5.4.2 "Effects on costs").

5.4.1.2 Utility in patients treated with biologics

5.4.1.2.1 Treatment effect

The Southern Swedish biologics registry (SSATG) has one of the longest follow-up of patients treated with biologics and 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[11]. The analysis included 2,554 patients with RA and showed a utility gain of around 0.25 after only 2 weeks' treatment which was 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[4].

Figure 5-4: Utility change with TNF inhibitor treatment in clinical practice[11]



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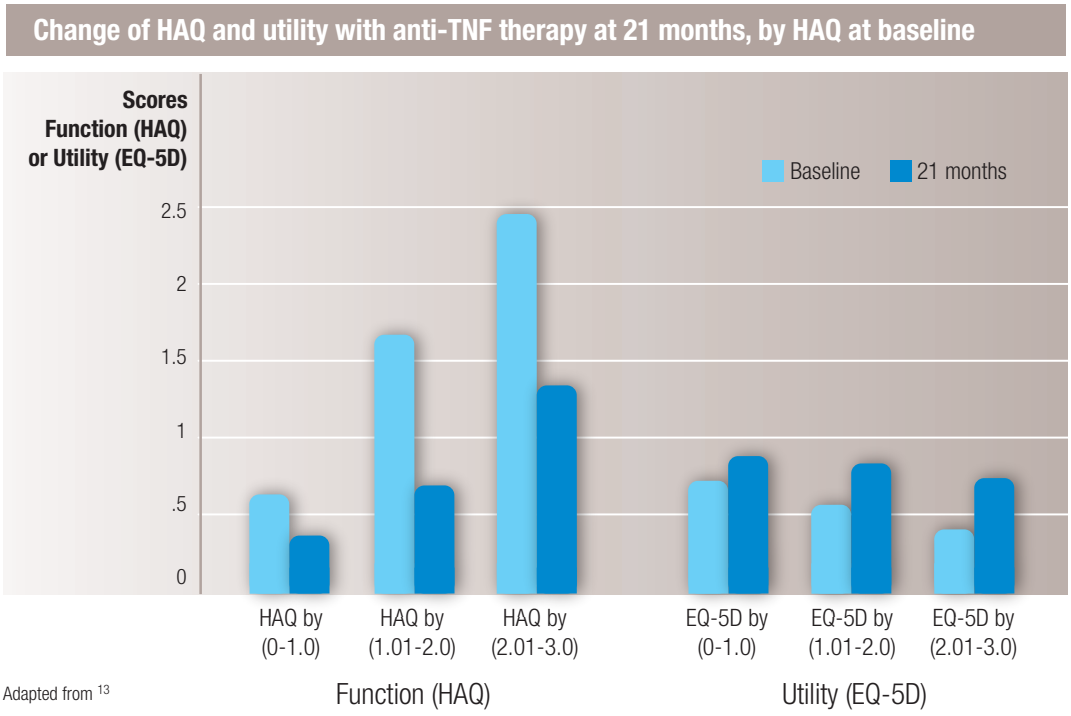
The change shown above for the large sample of patients in SSATG is lower than that first seen in the first 116 patients included in the registry. Compared to the full sample, these patients had considerably lower baseline utilities (0.28 versus 0.4). Although the full analysis found no significant temporal trend, i.e. the change was similar despite a slight increase in baseline utility over time[11], the low baseline of this early severe sample may explain the larger gain[4].

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. Indeed, joint damage is irreversible and thus limits the magnitude of the effect on utility that can be achieved with treatment. Given the finding of an irreversible part of HAQ in established disease[12] it is logical that utility, which correlates significantly with HAQ, would show an equivalent ceiling.

A recent analysis of 740 patients enrolled in the Alberta Biologics registry and treated with TNF inhibitors showed a similar utility improvement[13]. 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: HAQ and utility change after 21 months treatment [13]



Adapted from [13]

In the Swedish analysis (Figure 5-4), first and second line TNF inhibitor 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[14]. 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[15]. 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 individualised treatment and improved outcome. One 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 in Europe. By contrast, the average expenditure per QALY on new medicines by PHARMAC between 1998 and 2005 was only NZ$6,685 (€3,500), with an upper average expenditure per QALY in 2004 of NZ$15,768 and lower expenditure per QALY of NZ$3,000. These figures reflect the substantially lower willingness in New Zealand to invest in pharmaceuticals to obtain improved health outcomes as measured by QALY gains[16].

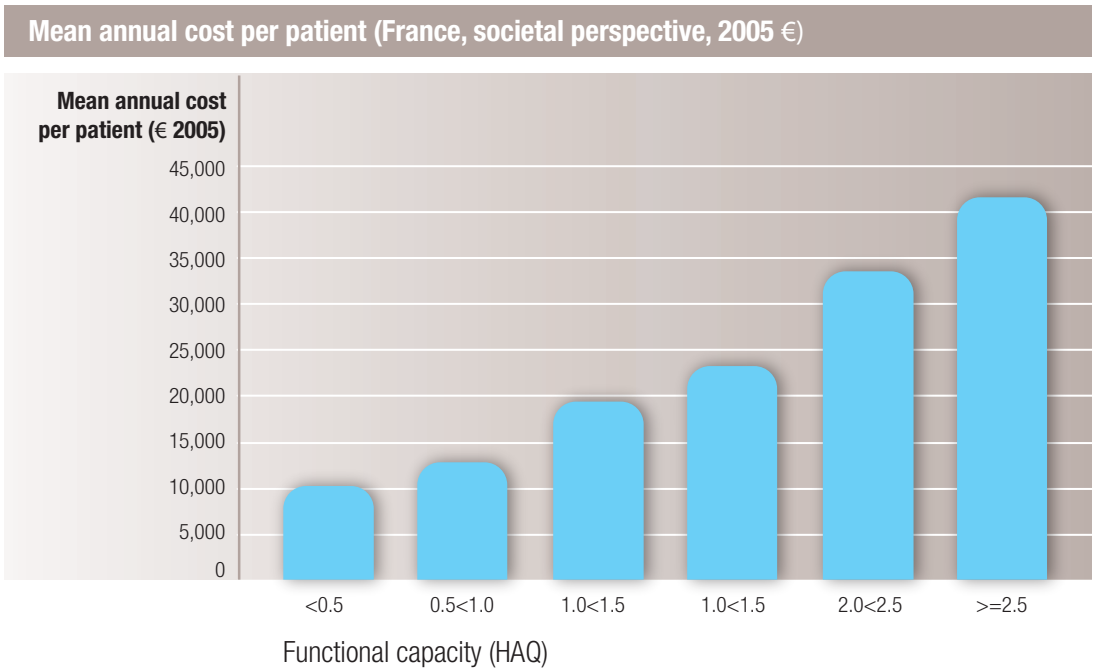
The value of an increase in utility by 0.20-0.25 and the maintenance at this level thus yields 0.20-0.25 QALYs every year for patients on treatment. Using the above unofficial threshold, the value of this improvement can then be estimated at around €10-12,500 per year.

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, whereas a full cost-effectiveness analysis would 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 therefore it is crucial to manage treatment in a way that avoids wastage as much as possible. One way is to introduce rules for stopping treatment when effectiveness is not fully adequate, which has been recommended in a number of European treatment guidelines. In the New Zealand situation, this would however require the availability and funding of more than one biologic agent to allow switching. Currently, one can expect that a number of patients remain on the one available treatment without experiencing the expected effect, which will lead to wastage. Effective treatment, used in the right patients and at the right time, improves health status, and with this comes reduction in the use of resources, both health care and other resources, leading to cost-offset.

5.4.2 Effects on costs

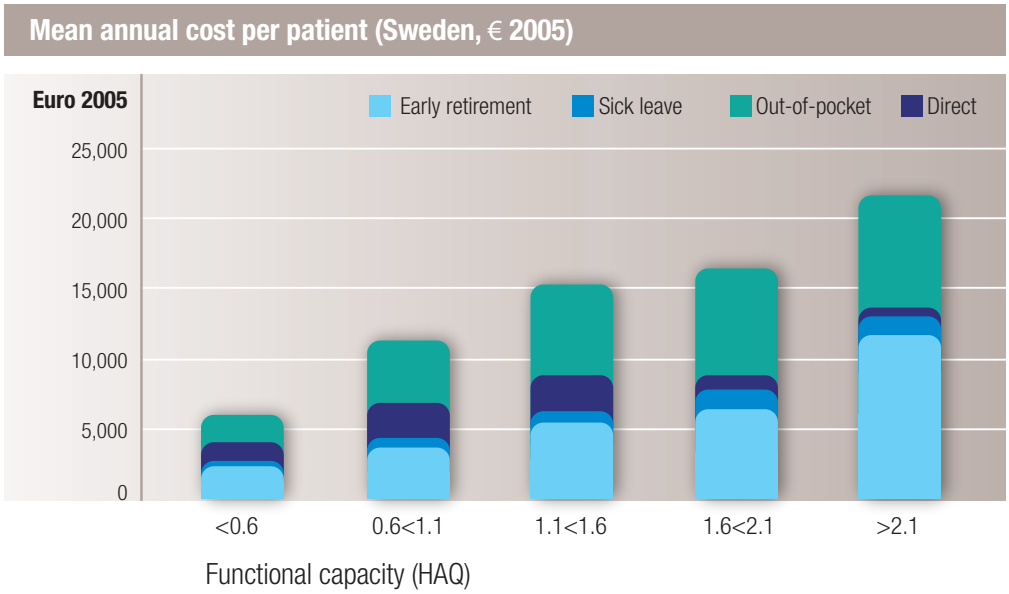
A number of studies have shown the correlation between HAQ and all type of costs. The largest and most recent comprehensive study from France clearly illustrates this relationship, but a number of earlier studies have shown similar results[7].

Figure 5-6: Relationship of costs to HAQ[7]



A similar study in Sweden investigated drivers of different types of costs[6]. 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 in Figure 5-7, 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[6]



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 in Figure 5-7, this would imply for most patients a move to a better HAQ category, and hence theoretically off-sets cost. 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 materialise in the long term. Patients on disability pensions may not be able to return to work for reasons other than their disease (general employment level, age, qualification, etc). Thus savings will come from avoiding patients having to leave the workforce in the first place. 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 first year analysis of the Southern Swedish Biologics Registry (SSATG)[4]. 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, hospitlisation 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.

Table 5-1: Reductions in costs in the first year of TNF inhibitor treatment[4]

	Mean costs per year (€, 2002) and utilities		
	Baseline mean (SD)	12 months mean (SD)	24 months (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)[i]	44 (52)	34 (44)
Total cost NSAID	117 (81)[i]	89 (87)	87 (87)
Total cost analgesics	63 (51)[i]	51 (49)	54 (50)
Total cost DMARD	289 (734)[i]	109 (387)	98 (343)
Total cost hospital	3823 (7179)[ii]	1963 (3839)	N/A
Total cost surgery	569 (989)	356 (675)	N/A
Outpatient visits[iii]	367	568[iv]	N/A
Acute care visits[iii]	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%
i usage at baseline, extrapolated to costs for the previous year
ii retrospective data, previous year
iii mean number of visits of the Lund cohort
iv including visits for administration of infliximab
** use during study year
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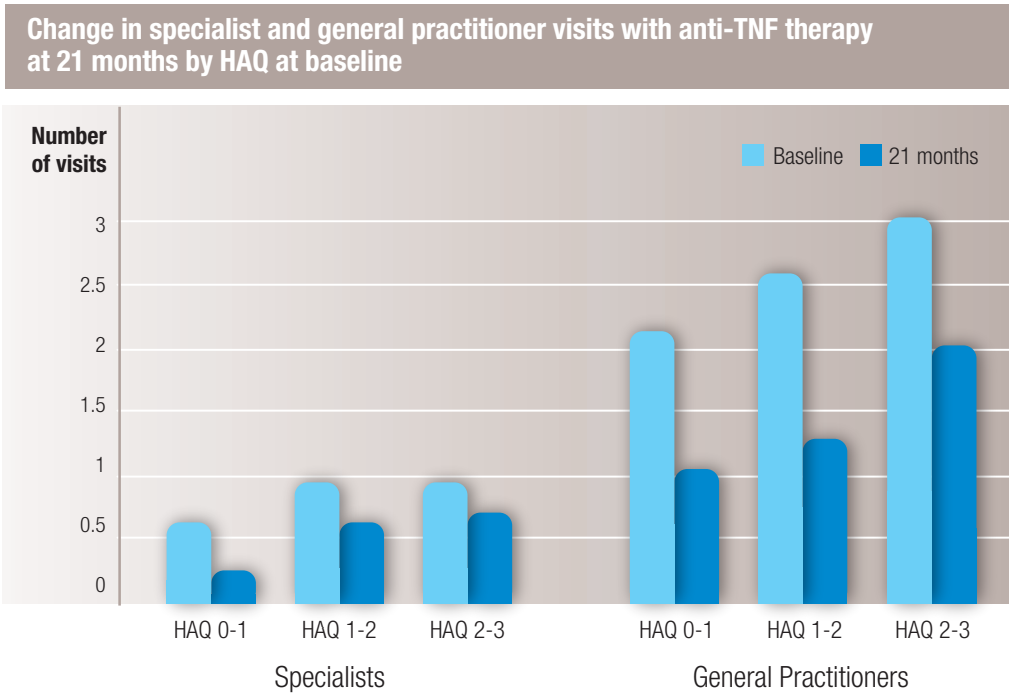
Similar findings were shown in a study designed to retrospectively assess drug utilisation and dosing patterns of TNF inhibitor therapy in 44 centres across Europe (DART study)[17]. The study included 739 patients with a mean disease duration of 15 years. Compared to the year prior, inpatient consumption 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[13]. The decrease was inversely related to the severity of functional handicap at baseline.

Figure 5-8: Decrease in outpatient consultations with TNF inhibitor therapy[13]



Reproduced from [13].

5.4.2.2 Indirect cost savings

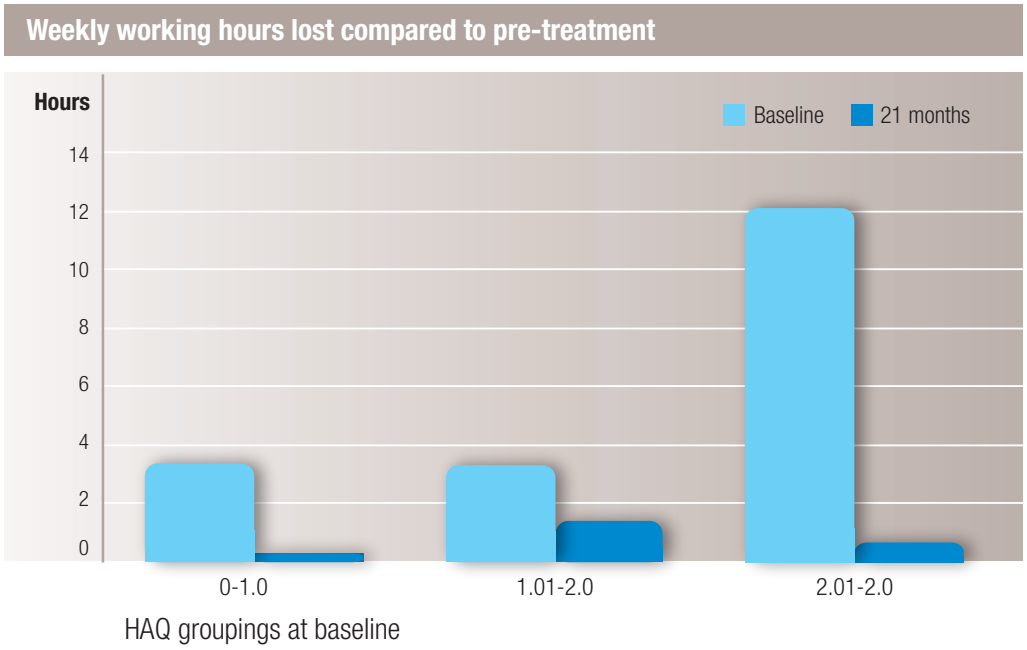
Indirect costs are resources lost due to a disease, such as the loss of work capacity. We distinguish short term losses (sick leave), and long term losses (loss of work capacity due to disease and premature mortality). They are costs to society rather than the health care system in terms of lost production, and are most often valued using the gender and age specific cost of labor 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 materialise and thus are the most difficult to show. Even ten years after the introduction of biologic treatments it is too early to measure their full impact on production losses. This is currently the most intensely researched 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 (refer to Table 5.1).

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

Figure 5-9: Weekly working hours lost by baseline HAQ[13]



Reproduced from [13]

A similar analysis was performed for the Stockholm biologics registry (STURE) and showed very similar results[18]. 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 a decrease in production losses of around 12% per year (based on average actual working time weighted by gender, equates to 36 hours in Sweden) and a reduction in production losses of around €3,500-4,000 per year.

A French study investigated the determinants of indirect costs in a mail survey performed with a patient association[19]. Mean age of respondents (N=1,189) 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 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 5-2: Risk factors for indirect costs[19]

Parameters	Odds Ratio for having indirect costs	Odds ratio 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 [19]

In cross-sectional samples, short term indirect costs represent around 25% of total production losses[7, 19]. 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 losing 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, although it is not always easy to separate these out. 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 and as treatment response is maintained it is reasonable to assume this will be maintained if treatment is continued.
- 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 modeling study based on 9-year follow-up data in the Southern Swedish biologics registry (SSATG)[20]. A total of 1,903 patients starting TNF inhibitor treatment were available, with 633 patients switching to a second and 170 patients to a third 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 than 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 5-3: Ten-year cost and QALY differences by HAQ at treatment start[20]

	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 subjective 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[21]). 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[22]. A Canadian meta-analysis estimated that the cardiovascular risk is increased by 50% in patients with RA[23]. 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[24]. Evidence is emerging that the cardiovascular risk is reduced in patients treated with biologics[25]. 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 far exist.

5.5 Conclusions

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

Evidence also notes that biological treatment increases the quality of life of the patients by increasing their functional capacity and lowering disease activity. Further, the higher quality of life level is maintained while remaining on treatment.

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Chapter 6 – Conclusions

The objective of this report was to assess the access to innovative treatment for rheumatoid arthritis (RA) in New Zealand and compare the results to Australia and the UK. The study builds on the previous work of *Access to innovative treatments for rheumatoid arthritis in Europe.*

RA is a chronic inflammatory joint disease, with an average onset in middle life that globally affects approximately 0.5-1% of the adult population. The burden of RA in terms of Disability Adjusted Life Years (DALYs) is, in contrast to other diseases such as cancer, driven by effects on disability rather than mortality. This can also be observed when comparing the mean utility (quality of life) of different diseases: RA is associated with one of the largest utility decreases. The burden in terms of DALYs and effect on quality of life in New Zealand and Australia is, as expected, similar to Western European countries.

Local data on prevalence and costs per patient were not comparable to data for European countries. Prevalence seemed to be considerably overestimated, with the result that costs were underestimated. The main comparison of prevalence in the current report was hence based on the methods used in the European report, where age and gender specific data for Northern or continental Europe were applied to the population structure in each country. Similarly, costs were estimated using the European cost model, where data can be imputed based on economic and health indicators to areas where there is no accurate local data.

With this method, both prevalence and costs resulted in similar estimates for New Zealand and Australia, compared to the UK, although production losses constituted a larger proportion of total costs. Using local data resulted in considerably lower costs per patient in Australia whereas in New Zealand, the costs remain on a similar level but with direct health care costs almost disappearing. The main reason for this is that the local data was retrieved from data bases that generally ignore a substantial part of costs, while the European estimates were mainly based on bottom up studies where data are collected directly from patients.

New Zealand had the lowest uptake of biological treatments for RA among the three countries compared, far lower than any of the Western European countries, and also substantially lower than Australia. A number of factors are likely to contribute to these differences. Prices in New Zealand are similar to those in the European countries, but with a somewhat lower health spend per capita, uptake of high priced drugs could be more difficult. However, taking into account national discounts to the drug reimbursement scheme in New Zealand may alter this conclusion, as this will drive prices lower. Thus, affordability is likely higher than estimated, and certainly does not explain the very limited uptake. Rather, one must conclude that it is a result of the restrictive reimbursement in terms of regimens covered, administrative hurdles for access and patient eligibility. To this must be added that New Zealand appears to have the lowest number of rheumatologists per patient population, as well as no clear treatment guidelines to ensure effective and continuous treatment for RA patients.

The clinical benefits of the biologic treatment in RA in terms of the effect on inflammation, function and quality of life are widely accepted. Data is also emerging on lower usage of some resources such as surgical interventions, acute visits and work absence, but these short term savings do not off-set cost of the biologics. In progressive diseases, economic effects can generally only be observed in the long term, as patients do not progress to severe disability or do so later. In light of this, the views on the cost-effectiveness of biologics in diverse countries differ, leading to more or less restrictive use. Our results indicate that New Zealand provides the most restricted access to biologics for patients with RA.

Notes

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