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Effectiveness and costs of new medical technologies –Register-based research in psoriasis

Jenny M. Norlin

Department of Public Health and Clinical Medicine, Dermatology and Venereology, Umeå University, Sweden
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In memory of my beloved grandmothers

Gunhild "Gunni" Marita Johanna Williamsdotter Olsson
and Astrid Norlin

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Abstract

Background Psoriasis is a chronic, immunological and systemic disease with an estimated prevalence of about 2-3 percent. Psoriasis is associated with the joint disease psoriasis arthropathy. There are several treatments options available for psoriasis and patients with moderate to severe psoriasis generally need systemic agents. In 2004 biologics were introduced for patients with moderate to severe psoriasis in Sweden.

The overall objective of this thesis was to assess the relationship between Health Related Quality of Life (HRQOL) and clinical outcome measures in psoriasis patients, to analyse the effectiveness of biologics in psoriasis in everyday clinical practice and to explore how costs of the psoriasis population changed after the introduction of biologics in Sweden.

Methods Research was based on national administrative registers and PsoReg, the Swedish registry for systemic treatment of psoriasis. In a cross-sectional study (paper I) the three outcome measures: the generic HRQOL measure EQ-5D, the dermatology specific HRQOL measure the Dermatology Life Quality Index (DLQI) and the clinical measure of skin involvement, Psoriasis Area and Severity Index (PASI), were analysed by demographic characteristics. The generic EQ-5D among psoriasis patients was compared to previously published values for the general population in Sweden. Relationships between measures were examined with correlation tests and regression analysis. A longitudinal study included patients registered in PsoReg who switched to a biologic agent for the first time during registration (paper II). The three outcomes EQ-5D, DLQI, and PASI were analysed before and after switch in the overall patient group and in subgroups. The relative effectiveness of continuing with the standard care of conventional treatment compared to switching from standard care to biologics was analysed in patients with moderate to severe psoriasis (paper III). Patients in PsoReg were matched with propensity scores and average treatment effects were estimated. The estimated outcomes were the change of EQ-5D, DLQI, and PASI. Patients were identified in national registers at the National Board of Health and Welfare when analysing costs; either by a registration of a psoriasis diagnosis in the national patients register and/or by a registration in the prescribed drugs register of a topical treatment with calcipotriol, a substance which has the indication psoriasis only (paper IV). Direct costs included patients' visits in specialist health care and prescribed drugs used for psoriasis treatment, retrieved from the national patients register and the prescribed drugs register, respectively. Indirect costs included productivity loss in terms of sick leave and disability pension, which estimated as excess costs compared to controls. Controls were selected from the normal

population and matched on sex, age and municipality. Productivity loss was estimated based on data from the Longitudinal integration database for health insurance and labour market studies at Statistics Sweden.

Results Patients with moderate to severe psoriasis had significantly lower HRQOL in EQ-5D than the general population (paper I). Women rated their HRQOL lower than men, even though men had more severe clinical skin involvement than women. (paper I). The generic measure EQ-5D and the dermatology-specific DLQI had moderate correlations whereas EQ-5D had low correlation with the clinical measure PASI (paper I). Patients who switched to a biologic agent during registration in PsoReg had significant improvements in all outcomes (paper II). Patients who fulfilled the criteria for moderate to severe psoriasis had the highest benefits of the biologic agents (paper II). The matched conventionally and biologically treated patients with moderate to severe psoriasis were essentially equal in important observable variables (paper III). The subgroup of patients not responding to conventional treatment had high potential benefits of biologic agents (paper III). Individuals with psoriasis had sick leave and disability pension to a larger extent than their matched controls (paper IV). Direct costs increased, whereas the indirect costs of productivity loss decreased between 2006 and 2009 (paper IV).

Conclusion Psoriasis is associated both with direct costs and indirect costs, and it has a negative impact on patients' HRQOL. When evaluating psoriasis treatments and making decisions about treatment guidelines, both generic, dermatology-specific HRQOL measures, and clinical measures are necessary; as they answer to different needs. Although dependent on data quality, generalisability, and current pricing, results suggest that conventional treatments are suitable as first line and biologic agents as second line treatment. Results indicate that the different types of systemic treatments are not allocated optimally among patients with psoriasis in Swedish clinical practice.

Key Words Psoriasis, Biologic Agents, EQ-5D, DLQI, PASI, Register-based research, Relative effectiveness.

Abbreviations

ATE	Average Treatment Effects
CPI	Consumer Price Index
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol Five Dimensions
HRQOL	Health Related Quality of Life
LISA	Longitudinal integration database for health insurance and labour market studies
NBHW	The National Board of Health and Welfare
NPR	National Patients Register
n.s.	Not statistically significant (p-values <0.05 were applied for statistical significance)
PASI	Psoriasis Area and Severity Index
PDR	Prescribed Drugs Register
PsA	Psoriasis Arthropathy
RCT	Randomised Controlled Trial
QALY	Quality-Adjusted-Life-Year

List of papers

This thesis is based on the following papers, which will be referred to in the text as paper I–IV:

Paper I

Norlin, J.M., Steen Carlsson, K., Persson, U. & Schmitt-Egenolf, M."Analysis of Three Outcome Measures in Moderate to Severe Psoriasis –A Registry Based Study of 2.450 Patients". *Br J Dermatol*. 2012 Apr;166(4):797-802. doi: 10.1111/j.1365-2133.2011.10778.x.

Paper II

Norlin, J.M., Steen Carlsson, K., Persson, U. & Schmitt-Egenolf, M. "Switch to Biologic Agent Significantly Improved Outcomes in Patients with Moderate to Severe Psoriasis". *Dermatology* 2012;225(4):326-32.
doi: 10.1159/000345715

Paper III

Norlin, J.M., Steen Carlsson, K., Schmitt-Egenolf, M. & Persson, U. "Relative effectiveness of new therapies using registers: Biologic vs. conventional agents for psoriasis" (Submitted)

Paper IV

Norlin, J.M., Steen Carlsson, K., Schmitt-Egenolf, M. & Persson, U. "Resource use in patients with psoriasis after the introduction of biologics in Sweden - Direct costs increase, whereas indirect costs decrease" (Submitted)

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Sammanfattning på svenska

Bakgrund Psoriasis är en kronisk, immunologisk, systemsjukdom som har en skattad prevalens på cirka 2-3 procent. Psoriasis är associerad med ledsjukdomen psoriasisartropati. Det finns flera behandlingsalternativ för psoriasis. Patienter med måttlig till svår psoriasis behöver i allmänhet systemiska läkemedemedel. Under 2004 infördes biologiska systemläkemedel för patienter med måttlig till svår psoriasis i Sverige.

Syfte Det övergripande syftet med avhandlingen var att analysera relationen mellan mått av hälsorelaterad livskvalitet och ett kliniskt mått av psoriasis svårhetsgrad på huden för patienter med psoriasis, att analysera effektiviteten av biologiska läkemedel för psoriasis i klinisk vardag samt att undersöka hur kostnaderna i psoriasispopulationen förändrats efter införandet av biologiska läkemedel i Sverige.

Metod Studierna baseras på nationella och administrativa register samt på PsoReg, det nationella kvalitetsregistret för systembehandling av psoriasis. Studie I var en tvärsnittsstudie baserad på PsoReg. Det generiska livskvalitetmåttet EQ-5D, det dermatologi-specifika livskvalitetmåttet Dermatology Life Quality Index (DLQI) och det kliniska måttet av psoriasis svårhetsgrad på huden, Psoriasis Area and Severity Index (PASI), analyserades i subgrupper av ålder och kön. Det generiska EQ-5D hos psoriasispatienter jämfördes med normalbefolkningen i Sverige. Relationer mellan utfallsmåtten undersöktes med korrelationstest och regressionsanalys. Studie II var en longitudinell studie som inkluderade patienter registrerade i PsoReg som bytte till ett biologiskt läkemedel för första gången under registreringen. Utfallen i det tre utfallsmåtten analyserades före och efter bytet till biologiskt läkemedel i den totala patientgruppen och i subgrupper. I studie III analyserades den relativa effektiviteten av att fortsätta standardbehandling med konventionella systemläkemedel jämfört med att byta från konventionell till biologisk systembehandling bland patienter i PsoReg med måttlig till svår psoriasis. Patienterna matchades med propensity scores och genomsnittliga behandlingseffekter skattades i de tre utfallsmåtten. I studie IV identifierades patientpopulationen i Socialstyrelsens register. Antingen genom registrering av diagnosen psoriasis i det nationella patientregistret och/eller genom registrering av en topikal behandling innehållande kalcipotriol i läkemedelsregistret. Kalcipotriol är ett ämne som används uteslutande för indikationen psoriasis. Direkta kostnader inkluderade patientbesök i specialistsjukvård från nationella patientregistret och förskrivna läkemedel som används för psoriasisbehandling, från

läkemedelsregistret. Indirekta kostnader inkluderade produktivitetsförluster i form av sjukskrivningar och förtidspensioner (sjukersättning) som merkostnader jämfört med kontroller från normalpopulationen, matchat på kön, ålder och kommun. Produktivitetsförlusterna beräknades baserat på data från den longitudinella integrationsdatabasen för sjukförsäkrings- och arbetsmarknadsstudier från Statistiska centralbyrån.

Resultat Patienter med måttlig till svår psoriasis hade signifikant lägre hälsorelaterad livskvalitet jämfört med normalbefolkningen (Studie I). Kvinnor rapporterade sämre hälsorelaterad livskvalitet än män, trots att kvinnor hade lägre klinisk svårighetsgrad av hudpsoriasis än män (studie I). De hälsorelaterade livskvalitetsmåtten, det generiska EQ-5D och det dermatologi-specifika DLQI, korrelerade måttligt. EQ-5D korrelerade dock dåligt med det kliniska måttet PASI (studie I). Patienter, som bytte till ett biologiskt läkemedel under registrering i PsoReg, hade betydande förbättringar i alla utfallsmått (studie II). Patienter som uppfyllde kriterierna för måttlig till svår psoriasis hade högst nytta av de biologiska läkemedlen (studie II). De matchade konventionellt och biologiskt behandlade patienterna hade liknade patientkaraktäristika i väsentliga och observerbara variabler (studie III). Den subgrupp av patienter som inte svarade på den konventionella systembehandlingen hade hög potentiell nytta av biologiska läkemedel (studie III). Sjukfrånvaro och förtidspension var större bland personer med psoriasis än bland matchade kontroller (studie IV). Direkta kostnader ökade och produktivitetsförlusten minskade mellan åren 2006 och 2009 (studie IV).

Slutsatser Psoriasis är förknippad med betydande direkta och indirekta kostnader och sjukdomen har en signifikant negativ inverkan på patienters hälsorelaterade livskvalitet. Vid utvärderingar av psoriasisbehandlingar och utformande av behandlingsriktlinjer behövs både generiska och dermatologispecifika hälsorelaterade livskvalitetsmått samt kliniska utfallsmått, eftersom måtten har olika användningsområden. Även om studierna är beroende av datakvalitet och generaliserbarhet, så tyder resultaten på att konventionella läkemedel är lämpliga som förstahands-behandling och biologiska läkemedel som andrahandsbehandling, vid nuvarande prissättning. Resultaten indikerar att fördelningen av de olika typerna av systemläkemedel inte är optimal i svensk klinisk praxis.

1. Introduction

The introduction of new, often costly, medical technologies, along with the demographic shift of an ageing population, put an increasing pressure on the public finances of health care in Sweden and elsewhere. New medical technologies often result in better clinical outcomes and improved health related quality of life (HRQOL) for patients. Nevertheless, resources are scarce and decision makers need to set priorities between different interventions and between different patient groups.

When a new medical technology is introduced health economic evaluations seek to analyse whether the medical intervention give "value for money", that is, to compare the new technology to the existing standard care in terms of both their costs and their consequences in health.

In the initial stages of implementing new medical technologies randomised controlled trials (RCTs) provide solid evidence to determine efficacy and safety, which is requested by regulatory authorities. Once the technology is used in clinical practice so called "real-world" data provide complementary information about the effectiveness in everyday clinical practice. Different terms are thus used to differentiate between the outcomes from RCTs (efficacy) compared to the outcomes in a real-world setting (effectiveness).

Real-world data reflecting everyday clinical practice is increasingly sought as the basis for treatment guidelines and reimbursement decisions. The information about the effectiveness, costs and usage of new medical technologies in everyday clinical practice is nonetheless often limited. Clinical and administrative registers are an underused source of information about real-world conditions.[1]

A recently introduced medical technology is biologic agents, biologics, for the chronic disease psoriasis. Biologics are a major technical advancement, nonetheless associated with considerable costs compared to the standard care of conventional systemic treatments. Clinical and administrative registers have been used in this thesis to highlight three issues that are of importance when a new medical technology is introduced.

The first issue concerns the relationship between disease-specific and generic outcome measures in patients with psoriasis. In RCTs disease-specific measures are required in order to determine the efficacy of the intervention. In health economic evaluations, however, generic measures are often preferred as they allow for comparison of different types of medical interventions and across different diseases and health care areas. Since the outcome measures may have implications for resource allocation, it is important to investigate how generic and disease-specific measures relate to one another.

The second issue concerns the real-world effectiveness and the usage of biologics in Swedish clinical practice. There are several factors that may have an impact on the effectiveness of a medical technology outside of the strict protocol-driven, experimental setting in an RCT. For example, patients in clinical practice are typically older and have comorbidities and physicians may individualise treatments for patients. As outcomes differ in real-world studies and RCTs, reimbursement decisions based on RCT may be inappropriate. Therefore, it is important to follow-up and analyse the effectiveness of medical technologies in clinical practice. Furthermore, when a new technology is introduced several barriers may exist to a broad implementation and treatment patterns can be expected to vary in clinical practice. In the early implementation phase patients with similar characteristics may receive different treatments. This phase is thus suitable to estimate the relative effectiveness of alternative medical interventions by matching patients with similar patient characteristics.

The third issue relates to how the overall resource use of the target patient population is affected by the introduction of a new medical technology. Primarily, it has an impact on health care budgets in terms of direct costs for the particular technology, but it may also have an impact on other health care resource use. For example, the use of other treatments, procedures and health care visits may decrease. Or, conversely, the "buzz" of the new technology may result in externalities such as an increased health care use of the patient population seeking new treatment opportunities. Moreover, new medical technologies may have a positive impact on patients' ability to work, that is, the productivity loss due to the disease may decrease.

This thesis is structured as follows: chapter 2 provides background information about the disease psoriasis (2.1), the background of health economic evaluations and cost of illness studies (2.2), background and challenges with observational research (2.3) and finally a background of outcome measures, effectiveness of biologics and costs in patients with psoriasis (2.4). The following chapters include the objectives of this thesis (3), the material and methods used (4), the main results (5) and a discussion of the findings, including policy implications and suggestions for further research (6). Finally, the overall conclusions are summarised (7). The original studies are enclosed as appendices.

2. Background

2.1. Psoriasis

Clinical background

Psoriasis is a common inflammatory skin disease. The prevalence varies around the world. In the Nordic countries the prevalence is about 2-3 percent,[2] which equals to about 200-300 thousand individuals in Sweden. Psoriasis is a systemic disease, meaning that it not only affects the skin but rather several parts of the body. Psoriasis arthropathy (PsA) affects between about 7 and 30 percent of patients with psoriasis.[3,4] Moderate to severe psoriasis has also been associated with cardiovascular disease,[5-7] crohn's disease,[8,9] depression,[10,11] and other comorbidities. Although much research remain about how the biologic mechanisms are related to one another.

There are several forms of skin psoriasis. Plaque psoriasis is the most common form. Other forms are guttate psoriasis, pustular psoriasis and inverse psoriasis. Psoriasis may also involve the nails. Erythrodermia is an uncommon form that covers most of the body skin surface. Acrodermatitis continua suppurativa is a rare pustular variant of psoriasis. Psoriasis fluctuates between periods of inflammation and remission. Psoriasis severity is related to seasonal variation as sunlight exposure reduces inflammation. Life-style choices, such as smoking and high alcohol consumption, may have a negative impact on the disease,[12,13] as well as obesity and stressful life events.[14,15] There is a strong genetic factor in psoriasis, were first-degree relatives increases the risk of developing psoriasis.[16,17]

Psoriasis has a major negative impact on health-related quality of life (HRQOL), which is not always in proportion to the clinical severity of the disease.[18-22]

Treatment

Psoriasis is a chronic disease with no cure, which often means life-long treatment for patients. The choice of treatment is determined by the severity of the disease and the medical history and preferences of the patient. The majority of people with psoriasis have mild to moderate disease, which can be treated with moisturizers, topical treatments with corticosteroids or calcipotriol, and with phototherapy. Patients with moderate to severe psoriasis often require systemic agents in order to manage their disease. The most common systemic treatment is methotrexate, which has been used for patients with psoriasis since the 1950's.

In 2004 biologic systemic agents, biologics, were introduced for patients with psoriasis in Sweden. Biologics consist of complex molecules that interfere with the immune system.[23] Biologic agents for psoriasis currently

registered in Sweden are etanercept, adalimumab, infliximab and ustekinumab. Etanercept, infliximab and adalimumab are tumor necrosis factor (TNF)-alpha inhibitors. Ustekinumab is an interleukin L12/23 inhibitor. All, but ustekinumab, had previously been approved for treatment of rheumatoid arthritis. Efalizumab was previously used, but it was withdrawn by the European Medicines Agency, EMA, in 2009 due to serious side effects. In Sweden current treatment guidelines suggests that biologics are to be used when patients do not respond to a conventional systemic treatment or when there is intolerance or contraindications to conventional treatments.[24]

All systemic treatments involve the risk of long-term side effects[25-28] and the risk need to be weighed against the benefits. The management of psoriasis generally starts with topical treatments and proceeds to systemic options if needed. Patients with moderate to severe psoriasis may use combination therapy or alternate between treatment options in order to maximise control of the symptoms and minimise the risk of side effects. The costs of biologic and conventional systemic agents differ considerably. Biologics cost approximately SEK 130.000 per patient and year and the most common type of conventional treatment, methotrexate, cost around SEK 1000 per patient and year.

2.2. Health economic evaluations and cost of illness

Health economic evaluations

As resources are scare, decision makers have to set priorities when allocating resources between different medical interventions and between different patient groups. In order to do so, decisions are based on multi-criteria decision analysis where health economic evaluations are one of the tools used. Health economic evaluations can be defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences" (Drummond et. al 2005 p.9).[29] Cost-effectiveness analyses are economic evaluations which relate the relative costs to the relative health gain of alternative interventions.[29] The health gain is quantified by some outcome measure which could be either a clinical outcome measure assessed by physicians or a HRQOL measures that are assessed by the patient. Cost-effectiveness analyses are expressed in incremental cost-effectiveness ratios (ICER), where the difference in cost is related to the difference in outcome. In cost-utility analyses the outcome is often measured with Quality Adjusted Life Years (QALYs), which take both the quantity and the quality of life into account. QALYs are calculated by using a generic outcome measure of HRQOL.

In Sweden there is no explicit cost per QALY threshold for the society's willingness to pay for a medical technology. The National Board of Health

and Welfare (NBHW) considers a cost per QALY below: <100 thousand a low cost, between 100 and <500 thousand a moderate cost, between 500 and <one million a high cost and >one million a very high cost. The Dental and Pharmaceutical Benefits Agency, TLV, is the Swedish government agency that determines whether a pharmaceutical product or dental care procedure shall be subsidised. TLV has accepted a cost per QALY threshold of about SEK 1 million in Sweden.[30]

Outcome measures

HRQOL assessments provide information about how a disease impact patients in psychological, physical, social, and functional well-being. These are domains that cannot be derived from clinical measures. HRQOL measures can be either specific for a disease, condition or treatment, or they can be generic. Generic measures include general dimensions such as pain, depression and daily function and can be used across medical conditions and health care interventions. Disease-specific measures include details that are specific to a disease or condition. Consequently, such measures are more sensitive to detect small changes in health outcomes than generic measures. Disease-specific measures are therefore suitable to measure clinically important differences in randomised controlled trials (RCT).

Generic measures provide a common unit of outcome for different interventions, which makes them preferable in health care policy. The generic measure EuroQol-Five Dimensions (EQ-5D)[31] is often favoured by reimbursement agencies and it can be used to calculate QALYs. Another feature of the EQ-5D is that it is preference-based as respondents are asked to (theoretically) give up something of value (e.g. money, time, lifetime) in order to avoid a particular health state. These preferences can be measured directly by the willingness to pay to avoid a health state, by standard gamble, where the risk of death is varied or by time trade-off where the time in health states is varied.[29] Preferences are, however, often measured indirectly by associating a health state derived by a questionnaire in the target population with previously estimated tariffs of preferences derived from the general population.[32]

Cost of illness

Cost of illness studies estimates the economic burden of a disease in society and enables comparison between settings or over time. Cost of illness studies can inform health policy makers about the extent of the economic burden of the disease. However, they cannot be used directly in priority settings as they do not evaluate strategies to reduce the burden of the disease.

Different perspectives may be adopted in cost of illness studies. When a strict health care budget perspective is applied, only direct costs are included. Direct costs include, for example, treatments, medical

consultations and hospitalisations. When a societal perspective is applied indirect costs are also included. Indirect costs are resources that are lost due to a disease such as the productivity loss that arises when patients are prevented from working. Productivity loss can be estimated with the human capital approach, which is the economic value of lost earnings. It can also be estimated with the friction cost approach,[33] which only includes the short-term productivity loss that arises before a job position is replaced with an unemployed worker or covered by a colleague.

In Sweden, it is recommended to use a societal perspective estimated with the human capital approach.[34] Studies sometimes include intangible costs, which are costs of pain and suffering. These costs are often omitted in cost of illness studies because of the difficulty to measure them in monetary terms. Intangible costs are more commonly captured with studies of HRQOL.

Cost of illness studies may differ by the methods used. For example, the applied perspective, sources of data, definition of the study population and the time frame used may differ.[35,36] Therefore, comparisons between different studies have to be made with carefulness.

2.3. Observational research

Observational research is non-interventional and non-experimental. Thus, investigators do not intervene by assigning treatment or additional diagnostic or monitoring procedures. Investigators rather intend to observe patients, treatments and events as they occur in routine clinical practice.

There are different types of observational research, such as cross-sectional studies, cohort studies, and case-control studies.[37] In cross-sectional studies one or more variables in a population are studied at one point in time. Cross-sectional studies may be useful for analysing associations between variables and for estimating prevalence of a disease. In cohort studies a specific patient group is followed over time, retrospectively or prospectively. Cohort studies can be useful to study incidence, the natural history of a condition and to observe longitudinal trends. In case-control studies cases that have a certain condition are compared to a control group with individuals who do not have the condition that is studied. Case-control studies aim to identify predictors of an outcome.

Observational studies provide different knowledge than RCTs

In RCTs the efficacy and safety of a medical intervention are investigated. An "experimental" setting is created in order to provide results with high internal validity, that is, the outcome of a trial can be attributed to the medical technology rather than to some other, confounding, factor. Consequently, RCTs aim at providing context-free knowledge. In regulatory

decision making, RCTs are essential as they answer to the question: “Can it work?”. Nevertheless, there is often limited knowledge about whether the benefits achieved by the average patient included in RCTs can be extrapolated to the average patient in a clinical setting.

Observational research can complement RCTs with information about real-world conditions. There are several reasons why medical technologies work differently in clinical practice, outside of the strict protocol-driven, experimental, setting of an RCT. Firstly, patients in clinical practice often differ from those included in an RCT. In clinical practice, patients are often elderly, have comorbidities or may have unusual clinical symptoms, whereas patients in RCTs are younger and “healthier” in the sense that they do not have unknown comorbidities that might bias results. Secondly, outcomes may be affected by variability in the skills and attitudes of physicians, the organisational settings and the extent to which health care is privately and publicly funded. In clinical practice, physicians may for example prescribe a drug off-label, that is, when a drug is used for an unapproved indication or in an unapproved patient group, which may result in a so called indication creep. Finally, the patient's degree of adherence to the prescription and patients’ life style choices may influence the outcomes.

Observational studies can provide knowledge about effectiveness, that is, whether a medical technology actually works in clinical practice. Well designed and well conducted observational studies have good external validity, which can make them generalisable for broad patient populations. They provide context-sensitive knowledge and answer to the question “Does it work?”. Observational studies are valuable for reimbursement decisions as they reflect everyday clinical decision making and treatment patterns.[38-40]

When there is no real-world data available other study designs are sometimes used. Advanced models may be set up as a complement to RCTs, in order to predict the real-world outcomes in the longer term, in different patient groups or in different settings. Cost-effectiveness analyses are sometimes performed by so called “piggy back” studies, where unit costs are added to the different events in a RCT. Reimbursement decisions based on such studies may be inappropriate as they generally do not reflect treatment patterns, health care visits, and outcomes among patients in clinical practice. The real-world outcomes may, thus, be different both from RCTs and from model studies.

Different study designs are useful for different research questions. All studies have their strengths and weaknesses and decision makers need different types of evidence to inform them about the appropriate use of interventions in routine clinical practice.[41,42]

The challenge of confounding bias

A large challenge to observational research is the possibility of confounding. Confounding factors are extraneous variables that are associated with both the outcome and the investigated treatment. Observational research can provide information about outcomes in a patient group before and after a medical intervention. These studies are descriptive in nature and cannot distinguish to what extent the difference in outcome is attributed to the investigated intervention or to what extent it is due to confounding factors.

The Average Treatment Effect (ATE) refers to the causal effect of a treatment. In RCTs we can assume that the difference between treated patients and their controls is the ATE as treatment was randomly assigned. The aim of the randomisation process is to make potential confounders affect cases and controls to the same extent.

In observational research, it is challenging to make causal inference. The ATE cannot simply be estimated as the average difference between patients with and without treatment because of confounding by indication. Confounding by indication arise if unknown factors that are associated with treatment assignment systematically differ between the patients with and without treatment.

There are statistical methods in order to reduce confounding when estimating causal effects. One method is to match treated cases with controls that have as similar pre-treatment characteristics as possible. The matching procedure attempts to resemble the randomisation process by matching the treated patients to controls who are comparable on all observed covariates. Instead of matching treated with controls on all possible variables, a propensity score can be used.[43,44] The propensity score is the conditional probability of being assigned a treatment, given a set of pre-treatment characteristics. Propensity score matching is widely used when evaluating labour market policies[45] and it is increasingly used in health economic research.[46] The propensity score can, however, only control for observed variables or to the extent that confounders correlate with the observed variables. Furthermore, there must be an overlap of the patient characteristics that are related to the treatment. That is, for each characteristic included in the propensity score there must be both treated and controls. If patients with a specific characteristic either always or never receive treatment, there would be no natural comparison group.

Well designed and well conducted observational studies can provide research with high quality. Confounding is, nonetheless, a challenge in all observational research and sensitivity analyses are essential in order to reduce this uncertainty.

Register-based research

Patient registers are increasingly used for observational research to support treatment guidelines and reimbursement decision making[47-49]. Patient registers may include a patient population with a specific disease or medical intervention. Register-based research allows for analyses of large patient populations over a long period of time. Generally, registers do not have required visits or interventions. Therefore, treatment patterns and resource use reflect clinical routine practice and include treatment options that are the relevant comparators in health care decision making. Moreover, as one treatment cannot be expected to be suitable for all patients, register data allows for analysis of specific subgroups of patients. An advantage of register-based studies is that they are relatively fast and inexpensive to perform compared to protocol-driven studies. Furthermore, register-based research can enable researchers to link data from a number of different registers, provided that unique, individual, identification numbers exists. Sweden has good administrative health care registers and social registers which can be linked by the personal identification numbers. These registers are an underused source of information to inform decision makers.[1]

2.4. Outcomes and costs in patients with psoriasis

Outcome measures in patients with psoriasis

Several clinical measures of skin involvement are available to assess the clinical severity of psoriasis. Psoriasis Area and Severity Index (PASI) is the most widely used measure[50] and it has been considered the gold standard to assess extensive psoriasis of the skin.[51] Clinical measures of skin involvement are essential to ensure efficacy of medical interventions, but the clinical severity is not always in proportion to the HRQOL in patients with psoriasis.[20,52,53] Therefore, patient-reported outcome measures of psoriasis are increasingly used in RCTs and observational studies in order to take the patient's perspective and HRQOL into account.[54] Various HRQOL measure in dermatology and psoriasis exists.[55] The Dermatology Life Quality Index (DLQI) has shown to be a valid measure in psoriasis[56-58] and it is commonly used in studies of the disease.[55,59]

As generic measures are essential in health economic evaluations, it is important that the disease's impact on HRQOL is captured by the measure. In mild diseases there may be a ceiling effect in generic measures if the majority of observations are clustered in one endpoint. Previous research of the generic HRQOL in psoriasis patients has mainly included the Short Form-36.[55,60,61] Although increasing, the use of the EQ-5D in psoriasis patients has been limited.[54] Only one previous study, based on a limited sample (n=35), has compared EQ-5D among psoriasis patients to the general

population.[62] In previous economic evaluations in dermatologic conditions so called "mapping" has been used when researchers have failed to include a generic measure in the original trial.[63,64] Mapping is used in order to "translate" a disease-specific value into a value of a generic measure.[65]

As the outcome measures may have implications for resource allocation decisions, it is essential to investigate how different disease-specific and generic measures relate to one another in a target patient population. Correlations between PASI and DLQI have previously been investigated in observational research,[52,66] but few studies, often with smaller samples, have assessed the relationship between EQ-5D and DLQI.[57,67]

Effectiveness of biologics in psoriasis

The efficacy of biologic agents has been demonstrated in several RCTs.[68-72] A recent study showed that about 30 percent of patients receiving systemic treatments for psoriasis in clinical practice would have been ineligible for RCTs.[28] This raises questions about the generalisability of results from RCTs to patient populations in clinical practice. There are few large-scale real-world studies of the effectiveness of psoriasis treatments; especially including the EQ-5D.[73]

In relative effectiveness studies outcomes of alternative interventions are compared in routine clinical practice.[74] Previous observational research comparing the relative effectiveness of biologic and conventional systemic agents in clinical practice is limited to two unmatched comparisons, including one cross-sectional comparison[75] and one that that lacks HRQOL outcomes.[76] RCTs of direct head-to-head comparison of biologic agents[77] as well as between biologics and conventional treatments[78,79] are also limited in psoriasis and analysis is restricted to clinical outcome measures of skin involvement.

Several barriers may exist to a broad implementation when a new technology, such as biologics, is introduced.[80-83] Treatment patterns in clinical practice can therefore be expected to vary in the early implementation phase. Consequently, as patients with similar characteristics receive different treatments this phase is favourable for estimating the relative effectiveness of alternative medical interventions using real-world data. Average treatment effects can be estimated by matching patients with similar patient characteristics.

Costs of patients with psoriasis

The recent introduction of biologics has had an impact on direct health care costs. Research about the cost-of-illness for psoriasis, including the impact of biologics, is non-exhaustive.[36] The severity varies largely among patients with psoriasis and accordingly the cost per patient differs between patient groups with different severity levels.[84-91] Furthermore, comorbidities such as

PsA and depression have shown to result additional direct costs and productivity loss.[92-94]

The total cost of the patient population with psoriasis in Sweden has not been previously estimated. Two recent studies in Swedish specialist care estimated the mean cost per patient with psoriasis. A study in 2009 estimated the monthly direct costs to €776 and indirect costs to €218,[90] which for 12 months equals to €9,312 and €2,616, respectively. A study in 2010 estimated the annual direct cost per patient to €2,169 and indirect cost to €1,230.[91] The difference in cost may be explained by the exclusion criteria of patients with biologics in the latter study. Furthermore, the former study was based on resources used during one month during the fall/winter when psoriasis of the skin tends to flare. Subsequently patients would be inclined to seek more health care than during other seasons.

Previous studies have suggested that psoriasis patients increased their working ability after initiating treatment with biologics.[95-97] The knowledge about productivity loss in patients with psoriasis in Swedish clinical practice is limited; in particular in relation to the introduction of biologics.[90,91]

3. Objectives

The overall objective of this thesis was to analyse outcome measures in patients with psoriasis, the effectiveness of biologics in psoriasis in everyday clinical practice and to explore how costs of the psoriasis population changed after the introduction of biologics in Sweden.

The objectives of the four papers were:

Paper I Firstly, to analyse EQ-5D, DLQI, and PASI in patients with moderate to severe psoriasis in Swedish clinical practice by demographic characteristics. Secondly, to compare EQ-5D scores in psoriasis patients compared to a defined Swedish general population. And thirdly, to investigate the relationship between the generic EQ-5D and the disease-specific DLQI and PASI measures.

Paper II To analyse the three key outcomes EQ-5D, DLQI, and PASI among biologic-naïve patients in clinical practice who switched from conventional to biologic treatments. Furthermore, to explore what patient subgroups benefit the most from biologics.

Paper III Firstly, to investigate the similarity of patient characteristics between patients with biologics compared to patients with the standard care of conventional treatments. Secondly, to estimate the relative effectiveness of biologics in HRQOL and clinical outcome measures by matching patients with conventional and biological treatments.

Paper IV To estimate costs of the psoriasis population in Sweden in 2006 and 2009 based on individual-level data from national registers and to analyse changes in costs between these years.

The papers are referred to as papers I–IV.

4. Materials and methods

4.1. Registers

PsoReg

PsoReg is the Swedish register for systemic treatment of psoriasis. The main objectives of the registry are to assess the long-term safety and effectiveness of systemic psoriasis treatments.[98,99] Conventional systemic treatments are also included in the registry. PsoReg started in 2006 and patients are registered at local, regional and university hospitals as well as in private practice and treatment centers driven by the patient organisation PSO. The inclusion criteria to PsoReg are that patients are diagnosed with psoriasis and use systemic treatment, or that they are prescribed systemic treatment at the time of registration.

PsoReg was estimated to include at least one registration per patient in about 65 percent of psoriasis patients with biologics and about 40 percent of psoriasis patients with conventional systemic agents in Sweden between 2007 and 2010.[100]

PsoReg includes background information about patient characteristics such as demographic characteristics, height, weight, tobacco and alcohol habits, age at disease onset, Psoriasis Arthropathy (PsA), different clinical types or symptoms of psoriasis, other previous diseases, family history of psoriasis, and treatments used previous to registration. Information about systemic treatments, values from different lab samples, examinations, and clinical and HRQOL outcome measures are continuously registered when patients visit the health care facilities.

National administrative registers

The national patients register (NPR), the prescribed drugs register (PDR) from the Swedish National board of health and welfare (NBHW) were used in paper IV to identify the study populations of patients with psoriasis in 2006 and 2009. NPR, PDR and the longitudinal integration database for health insurance and labour market studies (LISA) from Statistics Sweden were used to estimate direct and indirect costs for the identified populations. The registers collect data from regional and national administrative databases.

NPR includes specialist health care visits. Whereas inpatient care has almost complete coverage, about 80 percent of specialist outpatient care visits are registered with diagnosis codes.[101] Registrations are lacking in private health care and the quality of data differs between different regions in Sweden. The NPR does not include outpatient visits in primary care.

Since July 2005, the PDR includes all purchased prescribed pharmaceuticals in Sweden. The registered cost includes both the part paid by the patient and the reimbursed part paid by the county councils. Some over-the-counter drugs may be included if they were reimbursed. For instance, some county councils reimburse moisturisers for some severely ill psoriasis patients.

LISA includes data about income, unemployment, sick leave, disability pension etc., for individuals 16 years and older. The first 14 days of sick leave is not registered in national registers as these are employer financed and not part of the public social insurance.

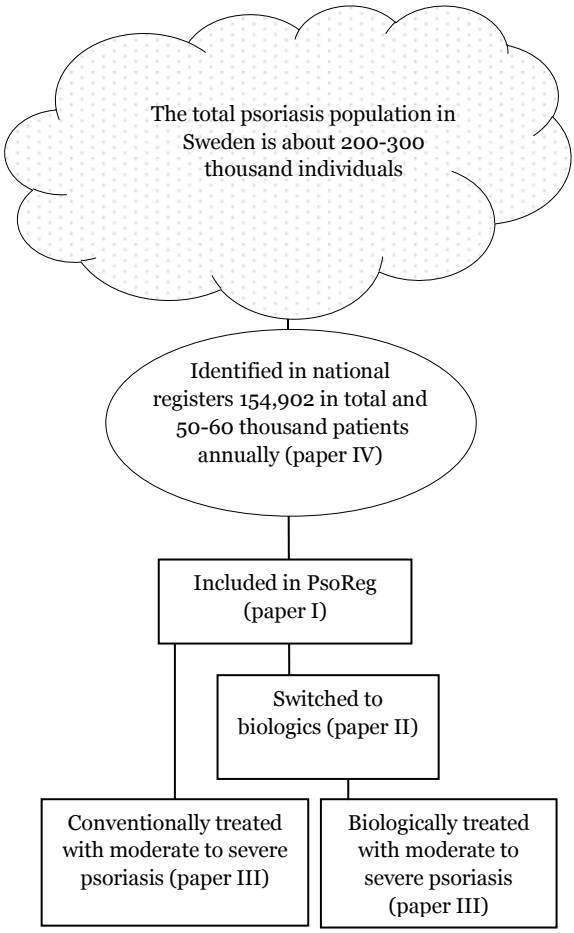
Data from the total population register at Statistics Sweden was also used to identify individuals who had re-used personal identification numbers. These individuals were excluded in order to avoid mix-ups. Date of death, if patients deceased during the study period, was retrieved from the cause of death register at the NBHW.

4.2. Study populations

Patients included in paper I-III were identified in PsoReg. The number of patients and observations is continuously growing in PsoReg. The total numbers of registered patients in PsoReg were 2,450 in June 2010 (paper I), 2,923 in May 2011 (paper II) and 3,663 in August 2012 (paper III).

Paper I was a cross-sectional study including all patients registered in PsoReg at the time of the study (n=2,450). Paper II included biologic-naïve patients who switched from conventional treatment to biologics during registration in PsoReg (n=267). In paper III biologically and conventionally patients who fulfilled the definition of moderate to severe psoriasis were included in the analysis. Patients who switched to biologics during registration, who had moderate to severe psoriasis pre-treatment and assessments of outcomes after switch (n=239) were included. Patients with conventional treatments who had at least two assessments and fulfilled the definition of moderate to severe psoriasis on their second last visit were included (n=378).

In paper IV costs were estimated for patients identified by the diagnosis code (ICD-10) in specialist care in the NPR or in the PDR by the code (ATC) for topical treatments including the vitamin D derivative calcipotriol. Calcipotriol is used for the indication mild to moderate psoriasis only. In total 154,902 patients were identified in national registers between 2004 and 2011. In paper IV the study populations included 52,135 patients in 2006 and 59,720 patients in 2009. The different study populations are illustrated in figure 1.



The majority of patients with psoriasis is treated in primary care and manages the disease with topical treatments. They are therefore not identified in national registers.

In total, 154,902 individuals were identified with psoriasis in national registers between 2004 and 2011. Paper IV included patients identified in 2006 (n=52,135) and 2009 (n=59,720).

Paper I was a cross-sectional study of all patients included in PsoReg (n=2,450).

Paper II included biologic-naïve patients who switched to biologics during registration in PsoReg (n=267).

In paper III biologically (n=239) and conventionally (n=378) treated patients with moderate to severe psoriasis in PsoReg were included.

Figure 1. Illustration of the study populations used in paper I-IV

4.3. Key outcome measures

Three outcomes measures were the main focus in this thesis; the generic EQ-5D, the dermatology-specific Dermatology Life Quality Index (DLQI) and the disease-specific measure of clinical skin involvement Psoriasis Area and Severity Index (PASI).

Euro-Qol Five Dimensions

The EQ-5D is the generic preferred by reimbursement decision makers, such as the TLV, for cost-effectiveness analyses. EQ-5D is based on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the three level (3L) version of the questionnaire,

patients respond how their HRQOL is today in three levels in each of the dimensions; (1) no problems, (2) some or moderate problems or (3) extreme problems[31]. For example, profile 11233 indicates no problems in mobility and self-care, moderate problems in usual activities, and extreme problems in pain/discomfort and anxiety/depression. Each health profile is associated with a utility weight. QALYs are calculated by weighting the time period in which a patient is in a certain health state, with the utility weight associated with that state. Thus, the utility of one year of perfect health is equal to one QALY and the utility of death is equal to zero.[29] As utility of death is equal to zero, it has been an issue of debate whether health states below zero are appropriate.[102-104]

EQ-5D is a preference-based measure as utility is derived from preferences by asking respondents to (theoretically) give up something of value (e.g. money, time, lifetime) in order to avoid a particular health state. Preference-based measures are favored over non-preference-based measures since there is a trade-off involved that may reveal the preferences respondents would have in reality.

Owing to the lack of available utility values in Sweden at the time of the study,[105] the UK tariff[32] was used. The UK tariff is widely used, which facilitates the comparison between studies. In the studies included in this thesis values negative values were set to zero in accordance with the previous study[106] that was used for comparison with a defined Swedish population. In a sensitivity analysis negative values were not set to zero in order to analyse what impact that had on results.

Disease-specific measures

DLQI is a non-preference-based measure that assesses patients' dermatology-specific HRQOL over the last week.[107] The DLQI questionnaire includes ten questions scored on a 4-point scale: not at all/not relevant (0), a little (1), a lot (2), and very much (3). The final summarised score ranges from 0 (best health state) to 30 (worst health state).

PASI measures the severity of the disease by assessing the extent to which body parts legs, trunc, arms, and head are affected and by the severity of the three main signs of psoriasis: redness, scaliness, and thickness. PASI results in a score theoretically ranging from 0-72, where a higher score is more severe psoriasis.[108] In clinical trials PASI75, which is a 75 percentage reduction of PASI, is often used as the endpoint.

Moderate to severe psoriasis is often defined as PASI>10 and/or DLQI>10, which is also used as the eligibility criteria for biologic agents in treatment guidelines.[24,109] Scores of PASI>10 and/or DLQI>10 are often referred to as the rule of ten. Sometimes over 10 percent of the measured involved body surface area is used instead of PASI>10.

4.4. Outcomes in patients with psoriasis

Relation between measures

Paper I was a cross-sectional analysis of the first registration of EQ-5D, DLQI, and PASI for each patient in PsoReg. Firstly, the outcomes were analysed by gender and age. Secondly, the EQ-5D among psoriasis patients was also compared to a defined Swedish population derived from a previous study matched on gender and age.[106] And finally, relationships between measures were examined with correlation tests and regression analysis.

4.5. Effectiveness of biologics in psoriasis

The effectiveness of biologics in clinical practice was assessed in paper II and paper III.

Effectiveness of biologics

In paper II the three outcome measures were analysed in biologic-naïve patients before and after switch to a biologic agent. The last observation before switch and the first observation after switch were used for each patient. An explorative analysis was performed to analyse what subgroups of patients benefit most from biologic agents, in terms of EQ-5D. The included subgroups were pre-treatment PASI and DLQI intervals of scores ≤10 compared to scores ≥10, patients who fulfilled the criteria for moderate to severe psoriasis compared to patients who did not fulfilled the criteria; patients with percentage change of PASI75 compared to patient who did not have PASI75; subgroups of different clinical characteristics of psoriasis (nail involvement, general pustular, palm pustular, non-palm pustular erythrodermia, and acrodermatitis continua suppurativa); and subgroups of the biologic agent first used.

Three sensitivity analyses were performed in order to explore whether results were robust. To begin with, the first assessments within the follow-up time 12 to 52 weeks was used for each patient; Secondly, patients who had discontinued the treatment with biologics on follow-up were excluded; Thirdly, patients with uncommon clinical characteristics (erythrodermia, general pustular, palm pustular, palm non-pustular and acrodermatitis continua suppurativa) were excluded. After the study was published, an additional sensitivity analysis was performed including EQ-5D values below zero.

The relative effectiveness of biologics

In paper III the relative effectiveness of biologics compared to the standard care of conventional treatments was estimated. Relative effectiveness was assessed by estimating average treatment effects (ATE) of three outcomes;

the relative change in EQ-5D, DLQI, and PASI between the two analysed assessments. Propensity scores[43] were used to match patients treated with biologics to patients treated with conventional systemic agents only in order to reduce confounding. The propensity score was estimated with a binary regression with the variable biologics/no biologics as the dependent variable. All available pre-treatment patient characteristics that were believed to affect either the treatment assignment or the outcomes, were included as independent variables. The included variables were: sex, age, psoriasis arthropathy (PsA), nail involvement, inverse psoriasis, koebner response, pustular psoriasis, pre-treatment PASI, pre-treatment DLQI, an interaction term between PASI and DLQI, debut age before 30 years old, whether patients where smokers, and whether patients where risk consumers of alcohol. Each treated individual was matched to one or several controls with the most similar propensity score. The relative effectiveness was estimated by the difference in average outcome among biologically treated patients and the average outcome among the matched conventionally treated patients.

The relative effectiveness of biologics was estimated both in the study population that actually received biologics (average treatment affect among the treated) and the conventionally treated patients who had not received biologics (average treatment affect among the untreated). In the analyses of average treatment affect among the treated the biologically treated were cases and the conventionally treated were used as controls. The controls were used to estimate the counterfactual situation of what would have happened if the biologically treated patients had not received biologics. In the analyses of average treatment affect among the untreated the conventionally treated were cases and the biologically treated were used as controls to estimate the potential benefits the conventionally treated patients would have if they received biologics. The difference between the two analyses depended on the patient population used as cases and the selection of controls. Several controls were selected as controls for each case, if there were several controls with similar propensity scores, and therefore the outcomes of the two patient groups differs.

A subgroup analysis was performed including conventionally treated patients who had moderate to severe psoriasis on both assessments. These patients were considered non-responders to the conventional treatments.

Several sensitivity analyses were performed. Firstly, a different matching algorithm, nearest neighbour matching, was used. Secondly, only observations within 12 months and 18 months between assessments before and after switch, or between the last two assessments, respectively, were included. Finally, the outcome change in EQ-5D was estimated without truncating values below zero.

4.6. Cost calculations

The cost of a defined population of patients with psoriasis in Sweden was calculated using a prevalence-based approach based on individual-level data from national registers. The identification of patients and linkage between registers are illustrated in figure 2.

Direct and indirect costs were estimated using different approaches. Direct costs included health care visits for psoriasis in specialist outpatient and inpatient care that were registered with psoriasis as a primary diagnosis in the NPR, and drugs relevant for treatment of psoriasis registered in the PDR. Drugs relevant for treatment of psoriasis included the WHO classified categories "D05 antipsoriatics for topical use", "D02 emollients and protective", "D07 corticosteroids, dermatological preparations", and the drugs with indication psoriasis under "L04 immunosuppressant's", including the biologic TNF-alpha inhibitors and the interleukin inhibitor.

No information exists in the PDR about for what indication drugs are prescribed. Biologics retrieved from the register may therefore be prescribed for other indications than psoriasis and PsA. The biologic agents etanercept, adalimumab and infliximab may be prescribed for other indications than psoriasis, such as rheumatoid arthritis, ankylosing spondylitis, juvenile arthritis, oligoarthritis, polyarthritis, crohn's disease, and ulcerous colitis.

The extent to which costs of biologics were due to psoriasis, PsA and for other diagnoses were therefore estimated based on the available information in national registers. Firstly, the costs of biologics prescribed from dermatologic clinics were calculated. These drugs can be assumed to be prescribed for the indication psoriasis of the skin. Secondly, patients who had PsA registered in the NPR, as primary or secondary diagnosis, were identified. The costs for the biologics, excluding those prescribed from a dermatologic clinic, among the PsA patients were calculated. Finally, the costs of biologics that were neither prescribed from a dermatologic clinic, nor for patients who had a PsA diagnosis were calculated.

Indirect costs included productivity loss, which was estimated by the incremental sick leave and disability pension compared to controls from the general population in Sweden, matched on sex, age and municipality. There were 15 controls in the data set, but the first five controls were considered sufficient for analysis. The productivity loss was estimated by using the human capital approach. The simplified assumption that people in ages 18-64 were working was made. The unit costs of a day/month on sick leave/disability pension were based on mean monthly wages from official statistics, matched on sex and age groups.

The LISA register does not include information about for what diagnosis patients were on sick leave or on disability pension. PsA is likely to account for a substantial part of the indirect costs and therefore a subgroup analysis

productivity loss of patients who had PsA registered as a primary or secondary diagnosis in the NPR the particular years were calculated.

Costs of patients with psoriasis were calculated for 2006 and 2009 in order to analyse changes in costs between these years. In order to make costs comparable between the two years, all costs in 2006 were inflation adjusted to the 2009 price level using consumer price (CPI) index, which was 5.44 percent during the time period. Sensitivity analysis was performed using other indices to adjust for inflation as prices in the health care sector may change differently than consumer goods in other parts of the economy. A health price index based on change in wages and prices from the Swedish Association of Local Authorities and Regions (9.58 percent) was used for direct costs and a wage price index from Statistics Sweden (11.6 percent) was used for productivity loss.

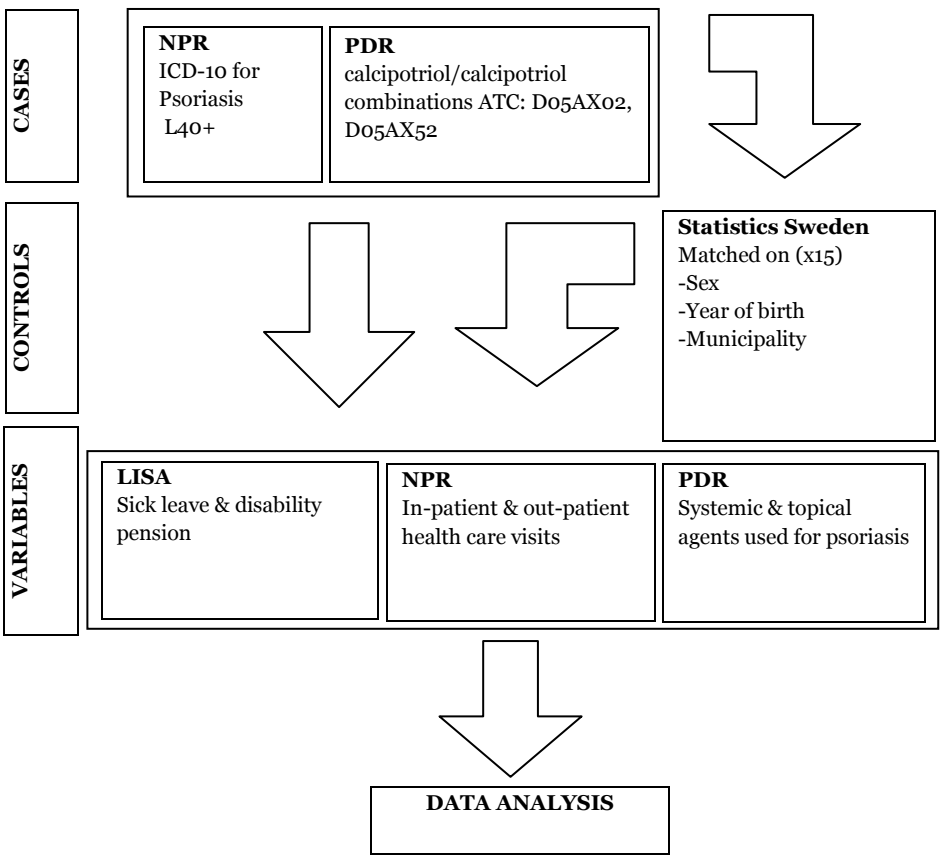


Figure 2. The linkage between the national patients register (NPR), the prescribed drugs register (PDR) and the longitudinal integration database for health insurance and labour market studies (LISA), used for the cost calculations in paper IV

4.7. Statistical analysis

A simple regression analysis of EQ-5D on DLQI and spearman's correlation test were used in order to analyse the relationship between measures (paper I). Correlations were categorised as very weak (0-0.19), weak (0.2-0.39), moderate (0.40-0.59) strong (0.6-0.79) and very strong (0.8-1) correlations in absolute values.[110]

As the outcome measures EQ-5D, DLQI, and PASI were non-normally distributed, non-parametric statistical tests were used. In order to test for differences between different patient groups in categorical patient characteristics the Mann-Whitney U test was used for two categories and the Kruskal Wallis-tests was used for three categories or more (paper I, II and III).

A Wilcoxon sign rank test was used to determine whether there was a difference in EQ-5D, DLQI, and PASI before and after switch to a biologic agent in the same patient group (paper II).

A simple regression analysis with EQ-5D as the dependent variable and sex, age, PsA, DLQI, and PASI as independent variables was performed in order to ensure that the explorative subgroup analysis was not driven by different distributions in sex, age or PsA (paper II).

A propensity score was used to match biologically and conventionally treated patients (paper III). The propensity score was estimated using a binary probit model with the outcome "biologic agent"/"no biologic agent" and the predicted value was the propensity score for each patient. The Pscore program in the Stata Statistical Software was used to test the balancing hypothesis.[111] The program identified the optimal number of blocks to ensure that the propensity score and the included variables were not different between patient groups. Differences in means in each block were then tested using two-sample t-tests. If the propensity score was not balanced, it was re-estimated with higher order terms.

The Psmatch program, as standard procedure, in the Stata Statistical Software was used to match patients and to estimate relative effectiveness in outcomes. Radius matching with replacement was used in order to limit the maximum difference between propensity scores and to allow for several matches. The radius matching may increase variance but decreases bias as it avoids bad matches.

The analytical standard errors were reported. These do not include the increased variance of the estimation of the propensity score and the imputation of the common support. Bootstrapping is sometimes used in the applied literature, but it is not clear whether bootstrapping is appropriate in propensity score matching.[112,113]

The difference in the presence of sick leave, disability pension and number of days in unemployment between cases and controls (paper IV) was

tested with t-tests. The difference in number of days in unemployment was tested as it may affect the number of possible days of sick leave and disability pension.

P-values <0.05 were applied for statistical significance. Statistical analysis was performed using Stata Statistical Software: Release 11.1 or 11.2. College Station, Texas, USA. Further details about the methods used, including propensity score matching, are reported in detail in papers I-IV.

4.8. Ethical concerns

This research was done in adherence to the Declaration of Helsinki guidelines and has been approved by the Umeå Ethical Review Board, Sweden. Patients registered in PsoReg gave their informed consent.

5. Main results

5.1. Outcomes in the cross-sectional study

Outcomes over subgroups of sex and age intervals

Patients with psoriasis had significantly lower HRQOL than the normal population (paper I). The mean EQ-5D was 0.76 in the psoriasis population compared to 0.84 in the normal population (figure 3). The values were statistically significantly lower for psoriasis patients in all age groups (p-value<0.001), except for the age group 80-88 years old (p-value=0.496).

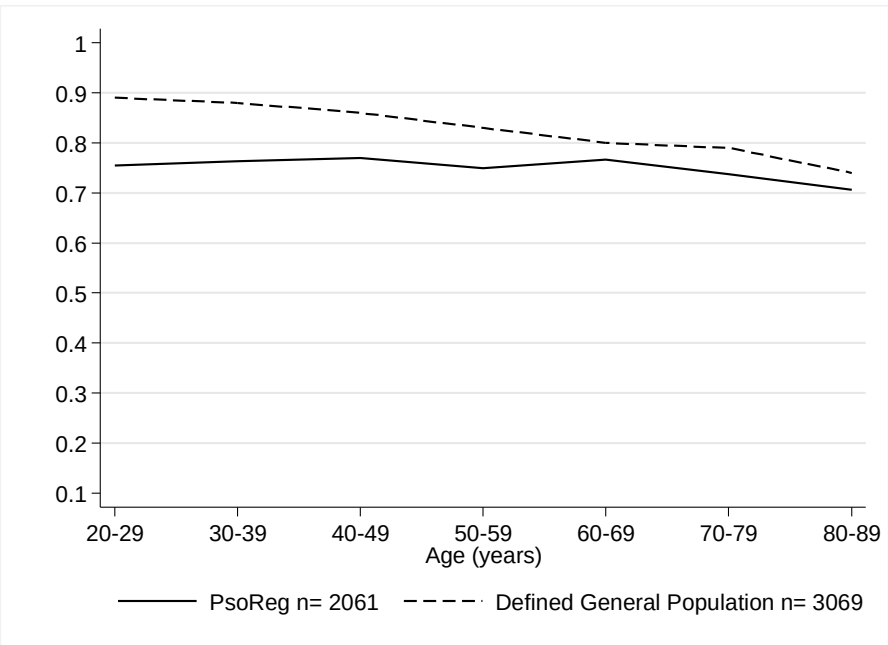


Figure 3. EQ-5D mean in the psoriasis population compared to a defined general population by age groups

Median EQ-5D, DLQI, and PASI scores in the psoriasis population were 0.77, 4 and 4.7, respectively. There was a trend that younger age groups had lower dermatology–specific HRQOL and more severe skin disease than older age groups, which was reflected by higher DLQI values and lower PASI values (p-values <0.001). Whereas older people in the normal population had lower overall HRQOL, reflected by the EQ-5D, there was no evident trend in psoriasis patients (p-value=0.136). In accordance with the general

population, women reported significantly lower HRQOL than men, which was evident in both dermatology-specific (p-value=0.003) and overall HRQOL (p-value<0.001). However, men had significantly more severe psoriasis measured in PASI (p-value<0.001).

Full health in the EQ-5D, that is no problem in any dimension, was reported by 27 percent of patients with psoriasis, compared to 46 percent in the defined general population.

Relationship between measures

The relationships between measures were in the expected direction. The correlation between the HRQOL measures, the EQ-5D and DLQI, and the correlation between the disease-specific measures, DLQI and PASI were moderate, whereas the correlation between EQ-5D and PASI was weak. The relationships between measures are illustrated in figure 4. All correlations were statistically significant (p-value<0.001). EQ-5D had a negative correlation with DLQI and PASI as a high value on EQ-5D indicates high HRQOL, whereas a high value of DLQI/PASI indicates a low HRQOL/severe disease. The correlation between EQ-5D and DLQI was stronger with higher levels of clinical severity of skin impact by PASI.

The simple linear regression with EQ-5D as a function of the total DLQI score was estimated to EQ-5D=0.88–0.02 DLQI. Thus, a one point increase in DLQI is expected to result in 0.02 fall of EQ-5D.

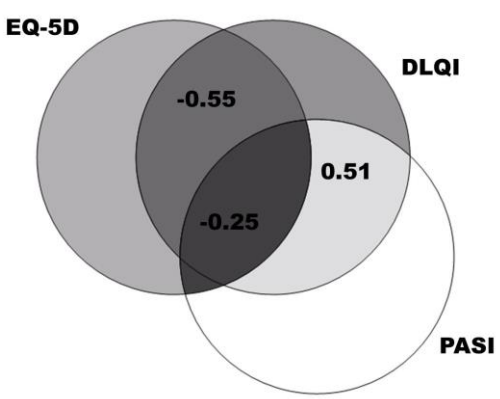


Figure 4. Illustration of the correlations (Spearman's rho) between EQ-5D, DLQI, and PASI

5.2. Effectiveness of biologics in clinical practice

Effectiveness of biologics

Psoriasis patients who switched to a biologic agent during registration had more severe skin involvement and lower HRQOL pre-treatment, than the overall psoriasis population included in PsoReg (paper II). There were statistically significant differences in all the outcome measures (p-value<0.001) between the observations before and after switch to a biologic agent (paper II). Mean change in EQ-5D, DLQI, and PASI were 0.12, -5.9 and -7.9, respectively. The subgroup that had the highest gain in terms of EQ-5D was patients that also had PASI75. Regression analysis suggested that the results in the subgroup analyses were not driven by sex, age or PsA as these variables were not statistically significant in the regression. Pre-treatment PASI (p-value=0.017) and DLQI (p-value<0.001), on the other hand, were statistically significant. An additional sensitivity analysis including EQ-5D values below zero did not change the main results. Only three values were below zero.

Patients who fulfilled the criteria for moderate to severe psoriasis

The majority of patients who switched from conventional treatment to biologics during registration fulfilled the criteria for moderate to severe psoriasis before the switch (76 percent in paper II and 70 percent in paper III). The explorative subgroup analysis showed that patients who had moderate to severe disease had a higher benefit of biologics, in terms of EQ-5D, than patients who did not (paper II). Patients who fulfilled the pre-treatment criteria for moderate to severe psoriasis had a mean change in EQ-5D of 0.14 and patients who did not fulfill the criteria had a mean change in EQ-5D of 0.03 (p-value<0.001).

The patient group of conventionally treated patients who also fulfilled the criteria for moderate to severe psoriasis on their second last assessment in the register accounted for 23 percent (n=378) of all conventionally treated patients with at least two registrations (paper III). A subgroup of ten percent (n=159) did not respond to the conventional treatments and had moderate to severe psoriasis on both visits.

Patient characteristics at the first assessment were similar in the two patient groups with moderate to severe psoriasis (paper III). There was no statistically significant difference in the distribution of sex. Among biologically treated 64 percent were men and among conventionally treated 58 percent were men. The distributions of risk consumption of alcohol, nail involvement, inverse psoriasis, koebner response and the outcome measures EQ-5D and DLQI were also similar (n.s). Mean EQ-5D was 0.64 in both treatment groups. DLQI was 13.3 and 12.9 among biologically and

conventionally treated, respectively. Patients who switched to biologics were somewhat younger; mean age was 48.5 compared to 52.8 years old among conventionally treated (p-value<0.001). Biologically treated had PsA to a larger extent; 38 percent compared to 26 percent among conventionally treated (p-value=0.002). Conventionally treated had pustular psoriasis to a larger extent: 12 percent compared to 5 percent among biologically treated (p-value=0.006). Conventionally treated also were smokers to a larger extent than biologically treated, 34 compared to 25 percent, respectively (p-value=0.019). A larger share of patients had their debut age with psoriasis before 30 years of age among the biologically treated compared to conventionally treated; 79 percent and 61 percent, respectively. Biologically treated also had higher PASI than conventionally treated; 14.9 compared to 10.4 (p-value<0.001).

Relative effectiveness of biologics

The conventionally and biologically treated patients with moderate to severe psoriasis were matched with propensity scores in order to estimate the relative effectiveness. Figure 5 below illustrates the common support of the propensity score in the two patient groups when the change of PASI was estimated.

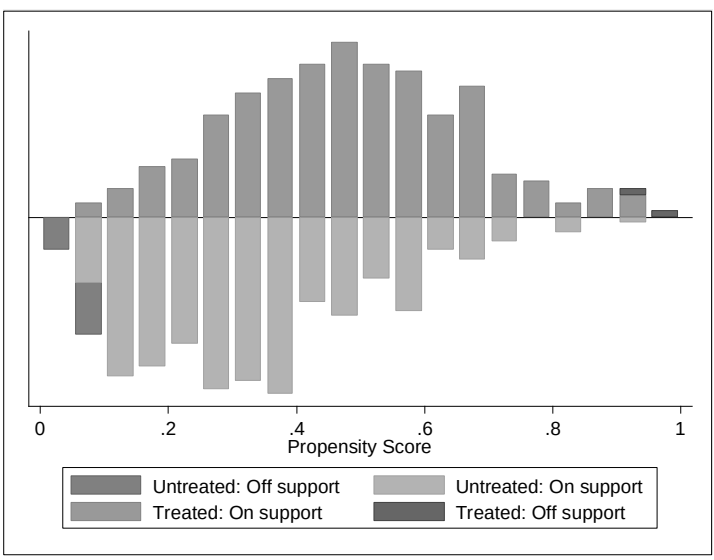


Figure 5. Common support of the propensity score with PASI change as outcome: Patients who switched to a biologic agent during registration (treated) and patients who only used conventional treatments (untreated)

The majority of patients, over 90 percent, fell within the common support, which suggests that conventionally and biologically treated patients were essentially equal in important observable variables. The common support was similar for all three outcomes.

The relative effectiveness of biologics, in the change of EQ-5D, compared to continuing with the standard care was about 0.11 among patients who received biologics. Among patients who did not receive biologics, the relative potential benefit of biologics were about 0.09. The relative effectiveness in change in DLQI and PASI were about -3.5 and -2.2, respectively, among biologically treated. The potential relative change in DLQI and PASI were 3.1 and 2.3, respectively, among conventionally treated.

In the subgroup analysis, where only including conventionally treated patients who had poor response to the conventional treatment, all three outcomes were higher than in the main analysis. The average treatment effect among patients who were biologically treated was then 0.15, -8.4 and -6.3 in the change of EQ-5D, DLQI, and PASI, respectively. The average treatment effect of biologics among patients who had not received biologics, that is, their potential benefit, was 0.15, -8.3 and -5.6 in the change of EQ-5D, DLQI, and PASI, respectively.

Sensitivity analyses showed results similar to the main analyses.

5.3. Costs in patients with psoriasis 2006 and 2009

Direct costs in patients with psoriasis

Costs and resource use in patients with psoriasis changed between the studied years 2006 and 2009. Total direct annual costs increased from SEK 348 to 459 million between the two years (figure 6). The costs of biologics accounted for the largest part of the increase in total direct costs. The number of patients who used biologics increased with 80 percent, from 1,233 to 2,227 patient, between 2006 and 2009. The majority of health care visits were in outpatient care. About one percent only was in inpatient care in 2006 and 2009. The total study population increased with 17 percent between 2006 and 2009.

Biologics prescribed from a dermatologic clinic accounted for about a third of costs of biologics in 2006 and in 2009. Costs of biologics in patients with PsA accounted for 60 percent and 54 percent of total costs of biologics in 2006 and 2009, respectively. The remaining costs for biologics, 11 percent in 2006 and 12 percent in 2009, were neither prescribed from a dermatologic clinic nor for patients with PsA.

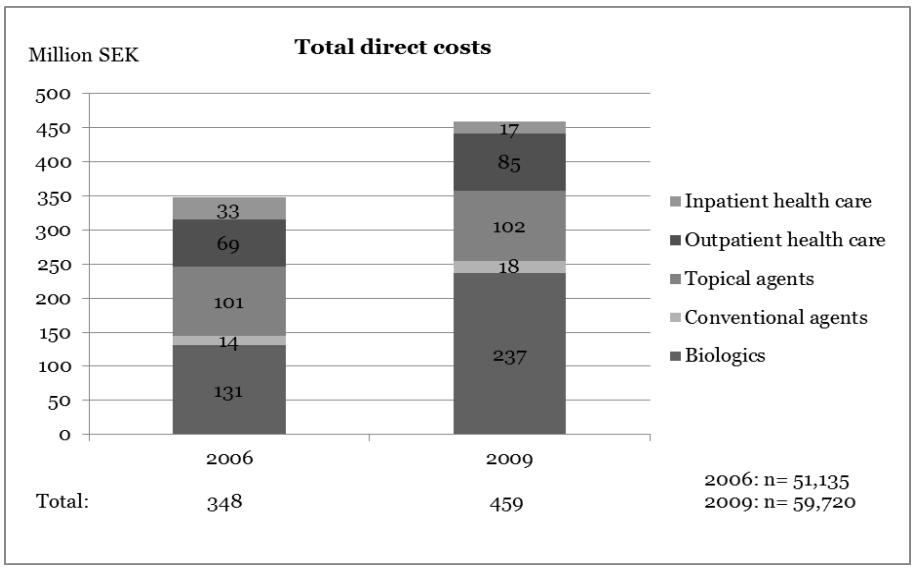


Figure 6. Total direct costs in 2006 and 2009

The mean direct cost per patient decreased for all treatment groups between 2006 and 2009. The mean direct cost per patient in 2006 was SEK 118,891, SEK 9,450 and SEK 3,055 for biologically, conventionally and topically treated, respectively. The mean direct cost per patient in 2009 was SEK 115,070, SEK 7,211 and SEK 2,838 for biologically, conventionally and topically treated, respectively.

Productivity loss in patients with psoriasis

Even though the study population increased between the analysed years, the total productivity loss decreased marginally from SEK 1,646 to 1,618 million between 2006 and 2009 (figure 7). The mean numbers of days of sick leave for patients with psoriasis were 25.6 in 2006 and 16.5 in 2009. The incremental numbers of days on sick leave, compared to controls, were 11.6 in 2006 and 8.0 in 2009. The mean numbers of months on disability pension for patients with psoriasis were 2.1 in 2006 and 1.9 in 2009. The incremental numbers of months on disability pension, compared to controls, were 0.8 in 2006 and 0.7 in 2009.

Overall, in the total study population, the percentage change in number of days on sick leave and months on disability pension changed to a smaller extent among the psoriasis patients than among their controls. The decrease in mean days of sick leave was 35 percent among cases and 39 percent among controls. The decrease in mean number of months of disability pension was 11 percent among cases and 11.6 percent among controls.

Among biologically treated However, the change in percentage was larger among psoriasis patients than among their controls, both regards to sick leave and disability pension. The decrease in sick leave was 58 percent decrease among cases and 14 percent among controls. Likewise, disability pension decreased more among biologically treated than among controls: 16 percent compared 10 percent.

In 2006, 17 percent of the total population had a PsA diagnosis in 2006 and 18 percent had PsA in 2009. These patients accounted for about half of the indirect costs each year (figure 7).

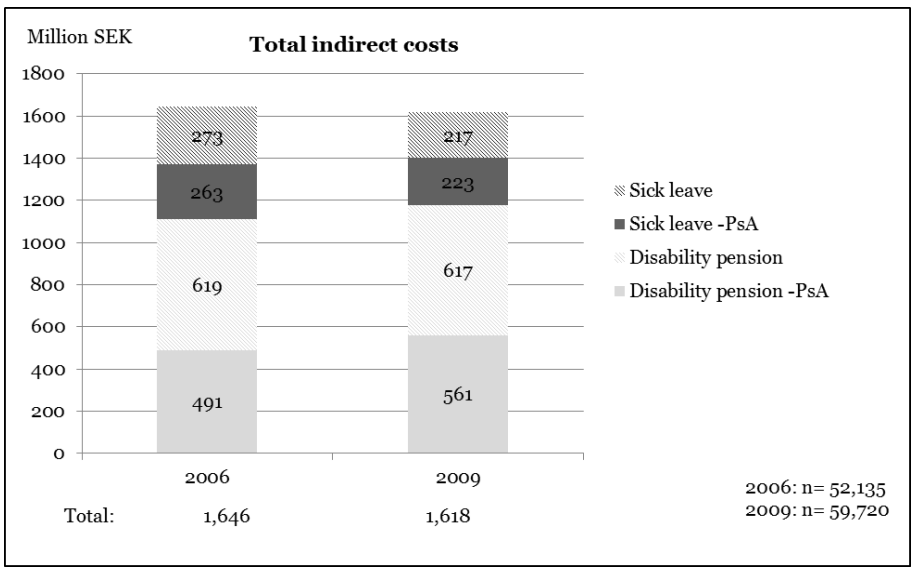


Figure 7. Total indirect costs in 2006 and 2009

The mean indirect cost per patient decreased for all treatment groups between 2006 and 2009. The mean indirect cost per patient in 2006 was SEK 123,943, SEK 64,594 and SEK 23,541 for biologically, conventionally and topically treated, respectively. The mean indirect cost per patient in 2009 was SEK 90,319, SEK 48,418 and SEK 20,141 for biologically, conventionally and topically treated, respectively.

6. Discussion

General discussion

Real-world data from clinical and administrative registers can provide knowledge about new medical technologies in clinical practice. Health policy makers need to understand that observational studies and randomised controlled trials (RCTs) can answer to different questions and that they have different strengths and weaknesses. RCTs have high internal validity and can answer questions about efficacy and short-term safety, which is essential in regulatory decision making. Nonetheless, results from RCTs generally do not reflect patients in clinical practice and may therefore not be possible to extrapolate to the average patient routine health care. Register-based studies, on the other hand, can have high external validity and can therefore answer to questions about effectiveness and long-term safety among patients in everyday clinical practice. As registers reflect patient's health-care seeking behavior, treatment patterns and outcomes in clinical practice, they can be useful for treatment guidelines, reimbursement decision making and decisions about resource allocation.

In clinical registers, such as PsoReg, it is essential to identify and include the key outcome measures that are useful in health technology assessment. The inclusion of the EQ-5D enables analysis of QALY gains of new medical technologies in clinical practice, which allows comparison with other medical technologies across disease areas. Disease-specific HRQOL and clinical measures are useful for physicians who seek to individualise treatments and provide optimal care for their patients. Including both generic and disease-specific measures in a register, also allows for scrutiny of the relationship between measures in clinical practice. In registers, there is a balance between including all desired outcome measures and questions, and the burden of reporting for physicians and patients. Extensive questionnaires increase the reporting burden and that may affect the data quality. Reporting bias may subsequently arise if particular information is systematically excluded by some physicians or patients. A strength of PsoReg is that the key outcomes are included; both generic, dermatology-specific HRQOL measures and clinical measures.

A strength of register-based research is that data reflect everyday clinical practice and thus contribute with information which cannot be obtained from RCTs. However, since there are no mandatory visits for patients included in registers as there are in RCTs, missing data and at what time measures are assessed cannot be considered to be at random. Causal inference in register-based research may therefore be challenging and results need to be interpreted with carefulness.

A limitation of register-based research is the uncertainty of whether included patients are representative for the overall patient population. PsoReg included approximately 65 percent of biologically treated psoriasis patients and about 40 percent of conventionally treated psoriasis patients between 2007 and 2010.[100] It was beyond the scope of this thesis to examine possible differences in patient characteristics and severity levels in patients who were included in PsoReg compared to those who were not included. Even though clinical registers may not have complete coverage of all patients, results provide information about a broad patient population in everyday clinical practice in contrast to the strict selected patient groups included in RCTs.

A relatively new method in register-based research is to perform randomised pragmatic trials, that is, randomly assigning treatments to patients in clinical practice.[114-116] Such study design may be useful in order to analyse the relative effectiveness of treatment options if RCTs suggests that there is no, or a small, differences between treatments. However, if RCTs suggest that there is a distinctive difference in outcomes, such method may seem unethical. In such cases, the relative effectiveness can preferably be estimated with matching methods, as in conventional and biologic agents analysed in the present study.[78] The matching method can identify the extent of the difference in relative effectiveness and furthermore, the proportion of patients that have potential benefits of a new treatment can be estimated.

Health policy makers need different types of evidence in their decision making. Study designs may range from strict protocol-driven RCTs, to randomised pragmatic trials, to propensity score matching methods, and to purely descriptive analysis. The different types of studies may answer to different questions. Register-based research can contribute in providing information about the usage of new medical technologies in clinical practice, including information about real-world effectiveness and usage in new patient groups.

Outcome measures (paper I)

Analysis of the relationship between the outcome measures suggests that EQ-5D, DLQI, and PASI are good complements. The moderate correlation between EQ-5D and DLQI indicates that both measures assess the same concept, HRQOL, but as the correlation was only moderate it suggests that they capture different aspects of the HRQOL. PASI had a weak relationship with EQ-5D. Yet, patients with moderate to severe psoriasis had significantly lower EQ-5D compared to a defined general population. This suggests that EQ-5D captures aspects of the disease that go beyond skin involvement and that PASI is not sufficient to capture the burden of psoriasis for patients. Hence, there is no “one single measure” that can answer to all needs on measurement of outcomes in patients with psoriasis. The different measures

are needed for different purposes. The EQ-5D is useful when evaluating biologics both in assessing the overall improvement of the patients' health and in policy makers' allocation of resources. Nonetheless, PASI and DLQI are necessary when evaluating efficacy, required by regulatory agencies as well as for clinicians individualising treatments and providing optimal care for patients.

Even though the validity of PASI has been shown in previous research, PASI can be affected by observer variation[117]. In RCTs the assessment is made by a few trained physicians, whereas PASI assessed in a national register of every day clinical practice is dependent on several assessing physicians. This is a limitation of using PASI in registers to assess clinical severity. The advantage is that it is widely used and familiar to physicians.

The use of HRQOL measures in psoriasis is increasing,[54] including the use of EQ-5D. Since our first two articles (paper I & paper II) were published a number of new studies have used and addressed the usage of EQ-5D in psoriasis.[118-121] A Belgian cross-sectional study, including over 3000 psoriasis patients, found that the mean EQ-5D and DLQI were 0.76 and 8.68,[118] respectively, which was similar to our results.

Three recent studies addressed the relationship between DLQI and EQ-5D, as well as the role of EQ-5D in dermatology. A review found a total of 19 publications about EQ-5D in dermatological conditions between 2003 and 2011, out of which seven in psoriasis.[119] The authors raise the question whether the EQ-5D is sensitive enough for usage in economic evaluations in dermatologic conditions. A study of treatment patterns among psoriasis patients in clinical practice suggested that both DLQI and EQ-5D should be included in clinical studies.[121] The conclusion in the latter study was in accordance with our findings. Although the EQ-5D is not as sensitive to change as DLQI, the EQ-5D is important to include in studies, especially when new treatment alternatives are introduced, in order to evaluate the cost-effectiveness of different treatment options.

A study that investigated the possibility to use mapping for transforming DLQI scores to EQ-5D, concluded that mapping between DLQI and EQ-5D had limitations in validity and clinical relevance.[120] Therefore, the authors suggested that the EQ-5D should be included in the original study. This is in line with our findings, that both clinical, disease specific and generic measures should be available. Nonetheless, in situations where the EQ-5D is not available, mapping may provide a second-best alternative that is better than completely lacking preference-based generic measures.

These recent findings are in accordance with our conclusion; that no outcome measure alone is sufficient to measure outcomes in patients with psoriasis. The three outcome measures EQ-5D, DLQI, and PASI complement one another and answer to different needs.

A recently published review study of RCTs of biologics in psoriasis found that the correlation between DLQI and PASI is higher in the severely ill patients that receive biologics.[122] Likewise, the correlation between EQ-5D and DLQI was stronger with higher levels of clinical severity of skin impact by PASI in our research. Consequently, mapping may be more appropriate in more severely ill patient groups.

Effectiveness of biologics (paper II & paper III)

The analysis of outcomes before and after switch from conventional treatment to biologics showed that clinical severity of skin involvement and HRQOL measures improved in psoriasis patients in a real-world setting (paper II). Clinically meaningful changes have in previous research of psoriasis been determined to changes of between 2.3 to 5.7 for the DLQI and between 0.09 to 0.22 for the EQ-5D.[57] Our results were within these ranges, both in the analysis of all patients who switched during registration in PsoReg (paper II) and in the relative effectiveness estimates compared to conventional treatment in patients with moderate to severe psoriasis (paper III). The change in PASI after switch (paper II) and the relative effectiveness in change in PASI (paper III) were lower than in previous research.[75-77,123] This is likely to be a consequence of wash-out periods before the introduction of biologics in many studies, which results in higher pre-treatment PASI scores.

The most common outcome in previous studies is the percentage of patients who reach PASI75, which is not comparable to the outcome studied in this thesis (paper II & III). Another difference is that in head-to-head RCTs patients have a wash-out period before the trial and the comparison is between switching from no treatment in baseline to a conventional treatment or to biologics. In this real-world study the comparison was between continuing with standard care with conventional treatment or to switch from standard care to biologics (paper III).

In one recent review study of long-term trials of biologics in psoriasis the authors conclude that various methods have been used in long-term analyses of biologics and that comparisons of agents are difficult without common standards for trial design and data handling.[124]

The largest limitation of estimating the relative effectiveness in observational studies is the possibility of confounding by indication. The patients who switched to biologics during registration in PsoReg may have unknown characteristics that systematically differ from conventionally treated patients. There was not enough longitudinal data in PsoReg at the time of analysis to know whether patients had moderate to severe disease over several occasions. It may not be enough to match conventionally and biologically treated patients based on the severity level at one point in time.

The propensity score can reduce bias, compared to unmatched comparison, by correcting for observed variables, while unobserved confounders can only be controlled for to the extent that they correlate with the observed variables.[43] Furthermore, as the included variables in registers are limited and predefined, which is also the case in RCTs, the possible variables to include in the propensity score are limited.

There are advantages of performing propensity score matching compared to using Ordinary Least Square (OLS) to control for confounders. Firstly, the balancing hypothesis makes sure that there are no differences in the distribution of the variables included in the propensity scores. Secondly, only patients within the common support are included, which is essential to maximise sample homogeneity and reduce the sensitivity to unobserved bias.[125,126] In the OLS procedure, the differences in distributions of variables and inclusion of data outside the region of common support may introduce bias when estimating the size of the effect.

Sensitivity analysis is an essential part of propensity score matching in order to investigate how the main results are affected by different selection criteria, matching algorithms, etc. By restricting the sample, the experimental situation is resembled to a larger extent, but at a cost of a decreased external validity.

There are several challenges when estimating average treatment effects using propensity scores in observational data, including selection of variables in the propensity score and choice of matching algorithm. These methodological challenges have been further addressed in previous research [40,112,127-130].

Costs in patients with psoriasis (paper IV)

The introduction of a new medical technology, such as biologics for psoriasis, may influence the overall health care resource of the wider patient population. The overall trend in the cost structure between 2006 and 2009 was that the direct costs increased, whereas the indirect costs decreased.

The total direct cost (in SEK 2009 price level) was estimated to SEK 459 million and the total productivity loss to SEK 1.6 billion in 2009. This can be compared to the annual cost of diabetes in Sweden in 2005 which was estimated to €168 million in direct costs and to €239 million in indirect costs[131] (approximately SEK 1.7 billion and SEK 2.4 billion, respectively in 2009 price level). The prevalence of diabetes has been estimated to about 254,000 individuals in Sweden,[131] which is similar to the prevalence of psoriasis. The incremental productivity loss for rheumatoid arthritis has been estimated based on national registers, similar to the methods used in this study. The productivity loss in 2007 was calculated to SEK 2.3 billion among 25,551 patients, compared to matched controls from the normal population[132] (approximately SEK 2.4 billion in 2009 price level). Another

example is the total cost of stroke in Sweden was estimated with an incidence approach to SEK 12.3 billion in 2000[133] (approximately SEK 14.1 billion in 2009 price level). The costs included outpatient visits, rehabilitation, drugs, and production losses due to early retirement and, unlike this study, due to premature death.

As the severity level of psoriasis patients is associated with the mean cost per patient, it is important to describe the severity level of the included patients. Severity levels in terms of PASI or DLQI scores were not available for the broad patient population included in this study. Therefore, the mean cost per patient was presented for subgroups of treatment types, which was retrieved from the PDR. The different treatment types (topical, conventional systemic treatments and biologics) can be seen as an indicator for disease severity. Among the subgroup of biologically treated patients, the mean direct costs per patient were similar in 2006 and 2009, whereas the productivity loss decreased with about a fourth between the two years.

In 2008 there was a reform which changes the sick leave policy in Sweden. This change complicates the comparison of indirect costs in 2006 and 2009 in the present analysis, as it is challenging to try to disentangle what part of the decrease that was due to the introduction of biologics. Noteworthy is that productivity loss decreased to a larger extent among biologically treated than among their controls between the analysed years.

The advantage of this study about costs in patients with psoriasis was that the national registers allowed for the identification of a broad psoriasis population, including patients with milder disease that were not included in PsoReg. Moreover, the strength of estimating the incremental cost in productivity loss compared to matched controls was that all productivity loss in patients with psoriasis could be captured, including costs associated with comorbidities. The human capital approach has been considered to over-estimate the cost of productivity-loss compared to using the friction cost method [134]. There are, to my knowledge, no studies comparing these methods in productivity loss of psoriasis.

A disadvantage of register-based research is the lack of detailed information which may have resulted in underestimates. For example, registrations of moisturises, which is an important part of psoriasis treatment,[91] was limited in the registers and there was no information about treatments or procedures in specialist care, such as costly phototherapies. An incomplete coverage of the patients register and the lack of a national primary care register may also have resulted in underestimates of costs of health care visits.[101]

Whereas health care visits are classified by diagnosis in the NPR, this is not the case for drug prescriptions and sick leave and disability pension. This is a limitation with the register-based approach. The included biologics are prescribed for other indications than psoriasis, such as RA, ankylosing

spondylitis, juvenile arthritis, oligoarthritis, polyarthritis, crohn's disease and ulcerous colitis. Previous research suggested that psoriasis account for only about 4 and 7 percent of TNF-alfa inhibitors in Sweden, whereas the remaining is in gastroenterology and, mainly in rheumatology indications.[80] The linkage between the national registers PDR and NPR overcame the lack of information about diagnoses to some extent. The cost of biologics prescribed from a dermatologic clinic, which can be assumed to be prescribed for skin psoriasis, was estimated to a third of total costs of biologics. About 54-60 percent of costs of biologics were prescribed for patients with a PsA diagnosis. The remaining 11-12 percent of costs of biologics may have been prescribed for other conditions that were not primarily associated with psoriasis. The linkage between the LISA register and the NPR showed that psoriasis patients with PsA were 17 and 18 percent of the total study population in 2006 and 2009 respectively, and accounted for about half of costs in productivity loss.

The casual mechanism behind psoriasis and the comorbidities of patients with psoriasis is unclear. Hence, the costs for the skin disease psoriasis and for the comorbidities in patients with psoriasis are difficult to disentangle. Nonetheless, this study shows that patients with psoriasis are associated with large direct and indirect costs.

Sensitivity analysis showed that the method used to inflate-adjust 2006 prices to the 2009 price level affected the results. By using a health care price index to adjust for inflation in direct costs and a wage price index to adjust for inflation in indirect costs, the direct and indirect costs increased. The method used to inflate-adjust prices complicates comparison between different years. Nonetheless, in this study it did not change the overall trends of the different costs.

Policy Implications

As the costs of the biologics are considerable compared to the standard care of conventional treatment, health care decision makers need to ensure that biologics are allocated to patients with the highest potential health gains.

Patients in the present study who fulfilled the criteria for moderate to severe psoriasis had larger benefits of biologics, in terms of change in EQ-5D, than patients who did not fulfill the criteria (paper II). In accordance the with current Swedish treatment guidelines,[24] these results suggest that at current price levels and assuming similar safety profiles of different systemic agents, conventional systemic treatments are suitable as first-line and biologics are suitable as second-line treatments for patients with moderate to severe psoriasis.

The results suggest that between a fourth and a third of biologically treated patients do not fulfill the pre-treatment criteria for moderate to severe psoriasis (paper II-III). Meanwhile, about ten percent of the

conventionally treated patients with at least two registrations in PsoReg had moderate to severe psoriasis and poor response to the conventional treatment (paper III). These patients, who had similar observed patient characteristics as biologically treated patents, were estimated to have high potential benefits from biologics (paper III).

There may thus be both over- and under treatment with biologics in Swedish clinical practice. By reallocating biologics from milder cases to moderate to severe cases of psoriasis, there is potential for a higher level of health in the psoriasis population. The more severe cases would gain more health than the milder cases would lose. Consequently, the health gain in the total patient population could increase without increasing the budget (figure 8).

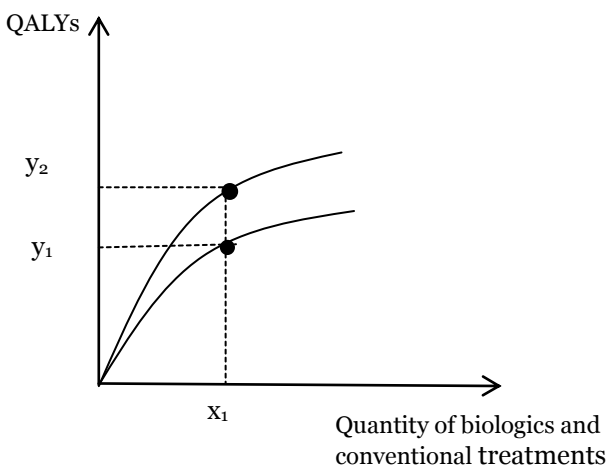


Figure 8. Reallocation of biologics from milder cases to the moderate to severe cases of psoriasis, could result in an upwards shift of the production frontier and an increase of the QALY gain in the total patient population

New biologic agents and bio-similars are likely to be introduced for patients with moderate to severe psoriasis in Sweden.[23] These agents can be expected to result in decreased prices for biologics. Once prices decrease, more patients can get access to biologics within the same budget restriction, and that could result in even higher levels of health in the psoriasis population.

Future research

Psoriasis has a considerable negative impact on patients HRQOL and poses an economic burden on society. Consequently, disease management and

costs of patients with psoriasis will continuously be of importance for health policy makers.

Our research indicates that some psoriasis patients may not receive the optimal level of systemic treatment in Swedish clinical practice. There may be several reasons for an uneven uptake of biologics:[82] physicians' lack of knowledge of the new medical technology, the high costs of biologics may be discouraging for health care providers, or there may be inequalities based on gender[135,136] or socioeconomic factors. Future research is needed about the determinants of treatment choice and the reasons for the possible sub-optimal allocation of systemic treatments among patents with psoriasis.

Furthermore, as patients in clinical practice are often exposed to a variety of treatments before response is achieved and treatments are often alternate in order to manage disease-control, more research about treatment patterns and long-term outcomes in routine clinical practice are needed.

Since treatment patterns, patient populations, and costs of patients with biologic treatments for psoriasis are likely to change over time, future register-based research should continue to follow-up the usage and effectiveness of biologics, as well as direct costs and productivity losses in patients with psoriasis in clinical practice.

7. Conclusions

Properly designed register-based research can provide valuable information about the usage and effectiveness of new medical technologies in routine clinical practice. This thesis finds that:

- Psoriasis has a negative impact on patients' HRQOL and that psoriasis patients have significantly lower HRQOL than the general Swedish population.
- A clinical measure of skin involvement is not sufficient to capture the burden of disease in patients with moderate to severe psoriasis. The outcome measures EQ-5D, DLQI, and PASI are good complements and they capture different aspects of the disease. All three measures are essential as they are used for different purposes including clinical effectiveness, treatment guidelines and resource allocation.
- Patients who fulfilled the criteria for moderate to severe psoriasis had greater overall health gains than patients who did not fulfill the criteria for moderate to severe psoriasis. Patients in clinical practice, with moderate to severe psoriasis, benefit from treatment with biologics compared to continuing the standard care of conventional systemic treatments.
- At current price levels and assuming similar safety profiles, the existing Swedish treatment guidelines, which suggests that conventional systemic treatments are to be used as first line and biologics as second line, are in accordance with these findings.
- The cost structure in the population of patients with psoriasis has changed after the introduction of biologics in Sweden. Direct costs have increased, whereas the productivity loss has decreased.

Moreover, this research indicates that the different types of systemic treatments are not allocated optimally among patients with psoriasis in Swedish clinical practice. More future research is needed about the possible over- and under treatment with biologics, and about the factors influencing it in Swedish clinical practice.

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