PsoReg – The Swedish Registry for Systemic Psoriasis Treatment

The Registry's Design and Objectives

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Key Words

Registries, psoriasis treatment • Psoriasis • Safety, psoriasis treatment • Quality assurance, health care • Ethics, medical • Drug therapy, psoriasis • Pharmacogenetics • Clinical trials, shortcomings • Treatment outcome, psoriasis • Clinical competence, tumor necrosis factor/therapeutic use • Professional-patient relations

Abstract

With the introduction of new systemic drugs for the management of psoriasis, we felt an obligation in Sweden to establish a trusted tool to monitor their use. We formed PsoReg to create a solid, long-term database in order to analyze safety and effectiveness of different systemic psoriasis treatment regimens. PsoReg will provide information to help clinicians individualize therapy on a rational basis through evaluation of effectiveness and adverse effects in specific patient subgroups. Designed and managed by specialized health care professionals, PsoReg will enroll all psoriasis patients on systemic treatment to allow a fair comparison of old versus new-generation psoriasis treatments. PsoReg will even create benchmark data for quality assurance of the medical service. A web-based design allows real-time pharmacovigilance and enables the registry to assist clinicians in their day-to-day management of psoriasis patients. In this way PsoReg can become an integrated part of tomorrow's dermatology.

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Introduction

If our psoriasis patients ask us which therapy we suggest, they believe that we will suggest the optimal therapy for the individual patient according to the best of our knowledge. The question is: How good is our 'best knowledge'?

PsoReg is a tool to continuously improve this knowledge through analyses of the experience of all participating physicians. Because PsoReg is designed and managed by dermatologists, the entire process of creating, analyzing, and finally applying the collective knowledge to patient care is done within our profession, and by design protected from commercial influences.

The high prevalence of psoriasis in Sweden, combined with the advanced state-run epidemiological infrastructure, gives us a unique possibility to perform advanced analyses and to apply the results to the national health care process. PsoReg will provide a systematic but real-life picture of the diseased population in actual practice and can compensate for the inherent shortcomings of both randomized clinical trials and spontaneous reporting of side effects which have been discussed recently [1].

The main objectives of PsoReg are to assess the long-term safety and effectiveness of systemic psoriasis treatments and to identify target phenotypes that may allow for specific, individualized treatments. By establishing benchmarks of psoriasis care, PsoReg will also serve as a quality assurance tool. To allow for a fair analysis, the observed rate of adverse effects in patients receiving biologics will be examined alongside the rate in patients receiving conventional systemic treatment.

The goal of PsoReg is to enable all physicians in Sweden who prescribe systemic psoriasis treatments to register and monitor their patients. However, to achieve our objectives with the shortest possible delay, a synthesis of results from registries across several countries is required. This synthesis becomes more efficient if the design of different registries is compatible. By publishing the PsoReg design in parallel to its launch, we want to stimulate the ongoing international foundation and collaboration of registries. In the light of the increased risk of infections and malignancies in rheumatoid arthritis patients treated with anti-tumor necrosis factor antibodies [2, 3], the production of reliable data for psoriasis is essential. An overview of the PsoReg is given in the appendix. The different pages of the registry described there (*Admission, Status, Treatment, Patient* and *Side effect report*) are referred to in italics in the text.

Design

To allow uncomplicated access, PsoReg is web based and can offer both real-time pharmacovigilance and practical support to clinicians in their day-to-day management of psoriasis patients. It is one question for a physician to be convinced about the significance of a registry and another question to use it on a daily basis. Established registries need to fight against doctor burnout, where physicians who initially used a registry drop out later on due to time pressure. Therefore, to succeed, a register needs to provide benefits to the user: Time invested in the registration needs a pay back. At this point, PsoReg's *Profile* provides a structured electronic medical record for psoriasis care, and statistical, reporting, and search functionality will follow shortly.

Safety

If adverse drug reactions (ADRs) escape detection in clinical trials, there is a risk that they will even escape spontaneous reporting for a longer period of time, a lesson we learned from the cyclooxygenase-2 inhibitors.

Conversely, as compared with the passive and unreliable system of spontaneous reporting, pharmacosurveillance with web-based registries is active and can recognize ADRs with the shortest possible delay. With PsoReg, we will be able to calculate the incidence rate of a given ADR, as we will know the number of affected individuals (the numerator) as well as the person-time at risk (the de-

nominator). Moreover, we will have the chance to allocate ADRs to specific patient subpopulations or situations.

However, even a registry can fail to detect side effects, if the physician does not suspect an event to be related to the drug given. Consequently, in PsoReg pharmacovigilance is taken one step further, as the physician is also prompted on the *Status* page to update the record as any new concomitant conditions develop. In the safety context, this question works as a concomitant disease surveillance module. In this way, PsoReg can identify new ADRs, even if the individual clinician perceives no relationship between a medication and an adverse event. On the other hand, a drug may provide an unanticipated beneficial effect beyond the labeled indication. For example, in patients with rheumatoid arthritis, methotrexate was found to decrease the cardiovascular mortality [4]. The concomitant disease surveillance module allows us to detect such positive secondary drug effects too.

Paradoxically, the psoriasis phenotype can radically worsen under a therapy given, like the new onset of psoriatic arthritis in individuals treated for skin psoriasis [5]. PsoReg is designed to sense even those changes, as the questions concerning the psoriasis phenotype on the *Status* page here work as a module for phenotype surveillance.

Effectiveness

Given their limited duration, randomized clinical trials can hardly address the long-term effectiveness of systemic psoriasis therapies. Furthermore, randomized clinical trials are often designed by drug manufacturers to establish the efficacy in the most efficient manner; this typically involves selection of a homogeneous patient population that is not necessarily representative of real-life practice [6].

Decision makers in health care, however, need more valid data sources. PsoReg is built to objectively detect opportunities for improved disease management in real life by comparing the long-term effectiveness of different treatments and treatment combinations. To assure the best possible evaluation, the effectiveness of the therapy is evaluated by the development of the disease over time as assessed by both the physician on the *Treatment* page and the *Patient* himself. Active involvement of the patient in this step does not only result in an improved judgment of the effectiveness, it even emphasizes the role of the patient as a partner in the disease management process. By combining on the *Patient* side the more disease-specific Dermatology Life Quality Index (DLQI) [7] with a generic instrument to measure the quality of life, the

EuroQol-5D [8], both cost-effectiveness and cost-utility calculations can be performed. Consequently, the disease burden of a psoriasis patient can be weighted against other diseases. In the future, those reliable data from the 'real life' may assure that our psoriasis patients have access to the best therapies available.

Individualized Therapy

Genetic evidence suggests that psoriasis is a heterogeneous disease [9]. This impression is corroborated by the dichotomy in therapy response between responders and nonresponders to a given therapy [10]. It might be possible that both risks and opportunities of different therapies can be attributed to patients with a specific profile. It is tempting to speculate how much more useful existing drugs could be, if we could predict a priori which patients are likely to respond optimally – and which patients have an elevated risk for adverse effects.

PsoReg collects considerable information on every registered patient in order to be able to search for particular patient profiles or constellations that are associated with good versus bad therapy responses and development of adverse events. As shown on the *Status* page (see appendix), special weight is placed on questions reflecting the known association of psoriasis with metabolic syndrome, smoking, and alcohol. For example, it is important to know whether patients suffering from obesity have a higher or lower risk of cardiovascular mortality under particular therapies.

Pitfall: Confounding by Indication

Biological therapies are quite new in the treatment of psoriasis. There is a clear need to compare effectiveness and safety of different biologics with each other and against conventional systemic treatments. However, even in a natural setting, this evaluation can produce misleading data, if not done carefully.

The likelihood for a given patient to receive a particular treatment depends on her/his psoriasis phenotype, comorbidities, and former treatments. However, these factors might be associated with adverse events in their own right. If a registry is not designed properly, it can consequently generate bias in the form of 'confounding by indication' [11]. This can be illustrated with the example of a patient who developed several nonmelanoma skin cancers after many years of both carcinogenic (PUVA) and

immunosuppressant (cyclosporine) treatments. A physician might for that reason choose retinoids for further treatment. However, in an inadequately designed registry, the development of the next nonmelanoma skin cancer could mistakenly be computed as a result of the retinoid treatment. To be able to correct for such a bias, PsoReg asks several questions concerning earlier therapies and diseases in *Admission* and *Status*.

Outlook

A well-designed registry is a win-win situation for all involved parties. From a societal perspective, the registry works to avoid unnecessary suffering and costs. The participating physicians and patients are reassured to incorporate medical progress by using new drugs, as they know they are part of a pharmacovigilance and effectiveness testing network dedicated to individualized therapy.

Appendix

Registration Flow

The first page of the register, *Admission*, needs to be filled in on the first visit only. The four consecutive pages, *Status*, *Treatment*, *Patient*, and *Lab values*, are filled in on every consecutive visit. The *Profile* pops up after the registration is completed. The *Side effect report* can be used on any given point of time.

Admission (fig. 1)

This page documents the age of onset and its circumstances and former psoriasis treatments and former (not ongoing) morbidities of special interest, such as lymphoma, skin cancers, and severe infectious diseases.

Status (fig. 2)

This form registers the patient's general health data. The selection of questions reflects the known association of psoriasis with metabolic syndrome, smoking, and alcohol. As the extent of psoriasis in the family is prone to change, this question is asked here and not under *Admission*. The physician is prompted to continuously update the concomitant diseases and the psoriasis phenotype as well as the current nonpsoriasis treatment.

Treatment (fig. 3)

The psoriasis drug the patient currently receives is chosen from a pull-down menu. After completing the

Patient ID 19 920728-2386	Register new contact	Complete latest	Side-effect report	Patient- profile	Log out	PSO REG
Administration v1.1.2481.28091						

Eva Smith

Admission	Status	Treatment	Patient	Lab values
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First name Eva	Last name Smith	☒ The patient has given formal approval.
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Earlier systemic treatments incl. UVB before registration in PsoReg <table style="width: 100%;"> <tr> <td>UVB</td> <td>No</td> <td>No. of months</td> </tr> <tr> <td>PUVA</td> <td>Yes</td> <td>12</td> </tr> <tr> <td>Methotrexate</td> <td>Yes</td> <td>6</td> </tr> <tr> <td>Retinoids</td> <td>No</td> <td></td> </tr> <tr> <td>Cyclosporine</td> <td>No</td> <td></td> </tr> <tr> <td>Adalimumab</td> <td>No</td> <td></td> </tr> <tr> <td>Alefacept</td> <td>No</td> <td></td> </tr> <tr> <td>Efalizumab</td> <td>No</td> <td></td> </tr> <tr> <td>Etanercept</td> <td>No</td> <td></td> </tr> <tr> <td>Infliximab</td> <td>No</td> <td></td> </tr> <tr> <td>Fumaric acid</td> <td>No</td> <td></td> </tr> <tr> <td>Hydroxyurea</td> <td>No</td> <td></td> </tr> <tr> <td>Thioguanine</td> <td>No</td> <td></td> </tr> </table>	UVB	No	No. of months	PUVA	Yes	12	Methotrexate	Yes	6	Retinoids	No		Cyclosporine	No		Adalimumab	No		Alefacept	No		Efalizumab	No		Etanercept	No		Infliximab	No		Fumaric acid	No		Hydroxyurea	No		Thioguanine	No		Onset of disease Age: 6-10 After: ☒ Throat infection ☐ Life crisis ☐ Medicine ☐ Unknown
UVB	No	No. of months																																						
PUVA	Yes	12																																						
Methotrexate	Yes	6																																						
Retinoids	No																																							
Cyclosporine	No																																							
Adalimumab	No																																							
Alefacept	No																																							
Efalizumab	No																																							
Etanercept	No																																							
Infliximab	No																																							
Fumaric acid	No																																							
Hydroxyurea	No																																							
Thioguanine	No																																							
Other earlier diseases <div style="border: 1px solid #ccc; padding: 2px;">Stroke SCC-Squamous Cell Carcinoma</div>																																								

Save

Fig. 1. Admission.

Patient ID 19 920728-2386	Register new contact	Complete latest	Side-effect report	Patient- profile	Log out	PSO REG
Administration v1.1.2481.28091						

Eva Smith – new contact

Admission	Status	Treatment	Patient	Lab values
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Date 9/20/2006	Type of contact Patient on visit	X-ray of lungs performed Yes Date: 1/1/2006	Pregnant No
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Height 160 cm	Weight 50 kg BMI = 19,5	Smoking ☒ Non-smoker ☐ Smoker Quit year:	Snuffing ☒ Non-snuffer ☐ Snuffer Quit year:	Alcohol Frequency: 2-4 times a month Amount: 1-2 drinks
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Psoriasis in family ☒ Mother ☐ Father ☐ Sibling ☐ Children	☐ Other relative ☐ No relative ☐ Don't know	Other current diseases <div style="border: 1px solid #ccc; padding: 2px;">E100 - Diabetes mellitus typ ...</div>	Other ongoing medical treatment <div style="border: 1px solid #ccc; padding: 2px;">Acet Acetylcystein 200 mg</div>
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Clinical type ☒ Plaque pso with guttate lesions ☐ Plaque pso without guttate lesions ☐ Erythrodermia ☐ Pustular psoriasis, general ☐ Pustular psoriasis, palmoplantar (PPP)	☐ Acrodermatitis continua suppurativa ☐ Palmoplantar non pustular psoriasis ☐ Inverse psoriasis ☒ Nail changes ☒ Koebner response
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Joint disease Psoriasis arthritis: No Morning stiffness > 30 min: No Sore/swollen joints: No
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Save

Fig. 2. Status.

dosage regimen, the treatment is displayed. In the case of combination therapies, all treatments can be displayed at once. The current disease activity, according to the physician, is registered by using both a visual analog scale (VAS) and the Psoriasis Activity and Severity Index (PASI).

Patient (fig. 4)

Here, the patient herself/himself is asked to quantify disease burden with the help of two VAS scales addressing disease activity in skin and joints. Additionally, a life quality instrument specific for skin diseases, the DLQI (Dermatology Life Quality Index), is employed alongside a generic instrument to measure the quality of life, the EuroQol-5D.

Patient ID 19 920728-2386	Register new contact	Complete latest	Side-effect report	Patient-profile	Log out	PSO REG
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Administration v1.1.2481.28091

Eva Smith – new contact

Admission	Status	Treatment	Patient	Lab values
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Current systemic treatment

Drug	From	Dosage	Interval	
Methotrexate 2,5 mg	10/19/2006	10 mg	once a week	<input type="button" value="Enter"/>

Medication	Inserted at	Dosage	Interval	
Methotrexate 2,5 mg	9/21/2006	10.0 mg	once a week	<input type="button" value="Withdraw"/>

Pso-skin activity

As a doctor, to what degree would you determine this patient's psoriasis?

no activity
|
3.4
 maximal activity

PASI	Area	Erythema	Induration	Desquamation
Head	0%	0.None	0.None	0.None
Trunk	<10%	1.Slight	1.Slight	2.Moderate
Arms	<10%	1.Slight	2.Moderate	2.Moderate
Legs	10-29%	1.Slight	3.Severe	2.Moderate

PASI = **7,0**

Fig. 3. Treatment.

Patient ID 19 920728-2386	Register new contact	Complete latest	Side-effect report	Patient-profile	Log out	PSO REG
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Administration v1.1.2481.28091

Eva Smith – new contact

Admission	Status	Treatment	Patient	Lab values
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Dermatology Life Quality Index

1. Over the last week, how itchy, sore, painful or stinging has your skin been?	<input type="text" value="A little"/>	7. Over the last week, has your skin prevented you from working or studying?	<input type="text" value="No"/>
2. Over the last week, how embarrassed or self conscious have you been because of your skin?	<input type="text" value="A little"/>	If "No", over the last week, how much has your skin been a problem at work or studying?	<input type="text" value="A little"/>
3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	<input type="text" value="Not at all"/>	8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	<input type="text" value="A lot"/>
4. Over the last week, how much has your skin influenced the clothes you wear?	<input type="text" value="A little"/>	9. Over the last week, how much has your skin caused any sexual difficulties?	<input type="text" value="A lot"/>
5. Over the last week, how much has your skin affected any social or leisure activities?	<input type="text" value="A lot"/>	10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	<input type="text" value="A lot"/>
6. Over the last week, how much has your skin made it difficult for you to do any sport?	<input type="text" value="A little"/>		DLQI index 13

EQ-5D

Mobility	<input type="text" value="I have no problems walking about"/>
Self-care	<input type="text" value="I have no problems with self-care"/>
Usual activities	<input type="text" value="I have some problems with performing my usual activities"/>
Pain/Discomfort	<input type="text" value="I have moderate pain or discomfort"/>
Anxiety/Depression	<input type="text" value="I am moderately anxious or depressed"/>

EQ-5D index **0,689**

Quality of life

On the line below, mark the location that best describes the severity of your **skin psoriasis (PsO)**.

no discomfort
|
3.1
 maximal discomfort

How much discomfort did you have last week due to your **joint disease (PsA)**?

no discomfort
|
0
 maximal discomfort

Fig. 4. Patient.

Patient ID 19 920728-2386	Register new contact	Complete latest	Side-effect report	Patient-profile	Log out	PSO REG
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Administration v1.1.2481.28091

Eva Smith

Reaction or event	Date of onset	Date ended	Ongoing?
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Description of reaction and event	Seriousness		
<input type="text"/>	Requires inpatient hospitalization		

Suspected medication	Action(s) taken	Append row	Delete
<input type="text"/>	Drug withdrawn		

Save Send report

Fig. 5. Side effect report.

Lab Values (not shown)

Lab values of special interest are registered here. In the future, this model will be completed from the referral management system/electronic patient record.

Side Effect Report (fig. 5)

The side effect report incorporated into the PsoReg can be forwarded digitally to the authorities. This is not only active quality assurance, but also a usability incentive which helps to integrate PsoReg into everyday care.

Profile (not shown)

The profile summarizes the medication along with the development of the disease over time. Individual patient contracts, such as smoking reduction, increased physical activities, and nutrition guidance, may be added. In addition, administrative information such as the time for the next consultation may be displayed. This profile can be printed and given to the patient at the end of the visit.

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