PSONET

EUROPEAN SURVEILLANCE NETWORK TO MONITOR THE LONG TERM EFFECTIVENESS AND SAFETY OF SYSTEMIC AGENTS IN THE TREATMENT OF PSORIASIS

DRAFT PROTOCOL

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OBJECTIVES

The main objective is to establish a network of independent European population registries, in order to perform coordinated post-marketing surveillance studies aimed at monitoring the effectiveness and safety of systemic agents, including biologicals (i.e. Tumor Necrosis Factor *alpha*, TNF-*alpha,* and T cell targeted molecules), in the treatment of psoriasis.

The network will achieve a critical mass of data through the development of a common methodological platform allowing collaborative analyses, enabling the conduct of investigations that would not be feasible in a single country registry. In principle, a wide range of analyses would be possible, including:

- Investigation of the clinical effectiveness of systemic treatments for psoriasis, in a population context;
- Identification of prognostic factors that can help in predicting the response to systemic treatments;
- Monitoring of adverse effects of systemic treatments, with particular attention to long-term and rare adverse events, including infections, lymphomas and other cancers.

Once the network has been established, it may be extended, with relative ease, to the monitoring of new therapeutic agents introduced in the future, and serve as a model for pharmacoepidemiology and independent post marketing surveillance in Europe. Moreover, the establishment of durable connections within a multidisciplinary group of European investigators sharing resources and activities may enable the nesting of biological studies within an epidemiological framework and the mounting of independent pragmatic randomised clinical trials to assess the advantages of different treatment strategies.

BACKGROUND AND RATIONALE

The prevalence of psoriasis in Europe is about 2-3%, and about 10-20% of affected patients have severe or complicated disease (Naldi, 2005). Thus, it is estimated that out of 815 million people in Europe (year 2000), 1.6 to 4.8 million persons suffer from severe psoriasis, a condition that has a dramatic impact on the quality of life of patients.

A genetic component in psoriasis is simply suggested by the fact that about one third of affected individuals reports a family history of the disease. In recent decades, a number of genetic loci have been associated with psoriasis and specific steps in disease development have been clarified. Physical traumas, acute infections, use of selected drugs (e.g. lithium salts) and stressful events can be triggering factors, and cigarette smoking and high body mass index are well recognized risk factors.

The treatment of psoriasis has long been based on laborious topical treatments that could assure, at most, a short term clearance of the lesions. Better control of disease activity could be obtained by more recently introduced treatment options, such as UVB phototherapy, PUVA therapy, methotrexate, ciclosporin and, in German speaking countries, of fumaric acid derivatives. However, the safety profile of these treatments is less than optimal, and they have thus been reserved to the treatment of moderate to severe disease.

In more recent years, a number of molecules which specifically target steps deemed to play a crucial role in the inflammatory process of psoriasis have been developed with the expectation of offering a more effective and less toxic treatment for psoriasis (Stern 2003). The molecules which are collectively named as “biologicals” since they are derived from live organisms or their products, include at this time agents that modulate T cell functions by acting on co-stimulatory molecules, e.g., efalizumab or alefacept and antagonists of the proinflammatory cytokine, tumor necrosis factor alpha (TNF-alpha), e.g., infliximab and etanercept. Infliximab, etanercept and efalizumab, have recently

entered the European market being registered by the European Agency on Medications (EMEA) for "treatment of moderate to severe plaque psoriasis in adults who do not respond or present contraindications or intolerance to other systemic therapies, including cyclosporine, methotrexate or PUVA therapy". Paradoxically, such an indication is not supported by firm evidence from available pre-registration clinical trials, where moderate to severe psoriatic patients were included without any consideration of previous response to conventional systemic agents. This may translate into patients treated with biological agents in Europe, who have a higher co-morbidty rate or are clinically more complex than patients studied in pre-registration trials.
The clinical experience on the use of biological treatments in dermatology is limited. Efficacy has been evaluated only in the context of placebo controlled randomized clinical trials lasting for no longer than 24 weeks.

With a few exceptions (e.g., PUVA therapy), medium to long term safety data derived from observational studies of systemic agents used in psoriasis are lacking. As far as biological agents are concerned, pharmaceutical companies are committed to set up phase 4 post-marketing programmes. However, these programmes do not seem to address the crucial issue of obtaining comparative safety data in a timely fashion and reliable estimates of rare events, as indicated by the examples below concerning studies planned for US approved biologicals (Stern, 2005):

Efalizumab - due 3/31/2014
Multicenter (500 sites) prospective
5–year surveillance study of patients who have received at least one dose of the drug

Alefacept - due 7/31/2010
5000-person study
After 2 years (March 2005), 657 enrolled

Etanercept – due 9/30/2013
2500 patients, not previously treated with etanercept

All malignancies and infection

The potential for rare but severe delayed adverse events of biological agents, such as severe systemic infections and selected cancers (e.g., lymphomas) has been suggested based on theoretical considerations and case reports (Hochberg et al 2005). More alarmingly, a systematic review using data from randomized controlled studies on the efficacy of anti-TNF antibody therapy (infliximab and adalimumab) in rheumatoid arthritis based on 3493 actively treated patients and 1512 patients who received placebo, found an increased risk of serious infections and a dose-dependent increased risk of malignancies, mostly lymphomas and basal cell carcinomas of the skin, in actively treated patients (Bongartz et al, 2006).

The study of the safety profile of systemic agents for the treatment of psoriasis is hampered by the fact that the risk factors for psoriasis are common to several other diseases, including several cancer types, that the disease itself may influence the risk of developing cancer or other severe diseases, and that generally, prior therapies may also lead to adverse effects. Thus, disentangling the effects due to biological agents from those due to shared risk factors, the disease itself or the effects of prior therapies is complex and only carefully designed studies, with large numbers of patients and entailing the collaboration of several experts from various disciplines (dermatologists, pharmacologists, epidemiologists, statisticians etc.) can provide useful information on the safety profile of biological agents. Moreover, even a national registry might not be able to provide meaningful information on rare adverse events in a reasonable time (Schimtt-Egenolf 2006).

Registries of biological treatments for psoriasis (and – for some registries – for other conditions, such as rheumatoid arthritis) have been established or are being activated in different European countries (Smith et al 2005, Schimtt-Egenolf 2007, Psocare 2004). Given the recent introduction of biological agents in the treatment of psoriasis, the registries have started very recently, or are in the process of being set up. There is hence a unique opportunity to establish a network to allow collaboration between the

different independent registries, in order to organize data collection in a fashion that will allow an easy pooling of data, as well as develop shared resources and activities with the aim of avoiding duplication of effort, maximising efficiency and sharing and spreading the know how.

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IMPLEMENTATION PLAN

General outline of the project

The project is composed of the following components:

- A survey of national registries of systemic treatments for psoriasis in Europe and establishment of an international collaboration;
- Implementation of study procedures to merge selected national data into an international database to be regularly updated;
- Conduct of analyses to assess specific safety issues for systemic agents used in psoriasis, including biological agents, with particular attention to rare and/or late events, e.g., infections, cancers, and interaction with other treatments and risk factors;
- Conduct of analyses to assess the comparative value of different systemic agents for the treatment of psoriasis and to assess prognostic factors for disease response and relapse.

An **International Coordinating Committee** will be established including representatives of national registries and, in some instances, national pharmacovigilance centres. The Coordinating Committee will be responsible for the overall monitoring of the project, including the definition of working groups on specific issues, the definition of data management and analysis, the approval of reports and published papers, privacy and ethical issues.

Survey of national registries

A survey of the organisation of registries of systemic treatments for psoriasis in different European countries will be conducted**.** The person responsible for each identified registry will be contacted and asked to complete a brief description of the organisation of the national registry (number of employees, sources of support, storage methodologies, entry criteria, variables collected and timing and modalities of follow up, and the number of patients included annually). Those registries satisfying pre-defined

organisational criteria will be further contacted and asked to participate in the international collaboration programme. An agreement to share selected data from the registry in the international collaboration programme over a pre-defined time interval should be signed by the registry manager.

Implementation of study procedures

Entry criteria and follow-up

The study population in the participating countries will consist of all the subjects with active psoriasis who receive, for the first time in their life, at least one single dose of a new systemic agent for psoriasis (the collection may be limited to biological agents in some countries). Only patients recruited within the national registries will be considered for inclusion. In addition, patients treated for rheumatological conditions by systemic drugs may be considered for inclusion for specific comparative analyses.

Common definitions for variables such as "disease severity" and "response to treatment" will be adopted. Uniform coding strategies should be better developed. Internal consistency checks will be also defined.

Follow up procedures implemented in the context of the different national European registries will be made as similar as possible. Active follow up (at least one contact per year) with minimum loss to follow up (less than 20%) will be aimed for.

Definiton of the minimum set of variables to be merged

Although each registry will decide independently on data collection and criteria for patient enrolment, a minimum set of data to combine in an international database will be defined in advance, as well as recruitment criteria and follow-up modalities.

The minimum set of variables to be shared among databases will include:

1. Patients' socio-demographic characteristics (age, gender, profession, marital status) personal habits (smoking, alcohol consumption), anthropometric variables (weight and height);

2. Psoriasis and its characterization (date of reported onset, date of diagnosis, type of psoriasis, maximum extent), previous systemic treatments (for each treatment modality, date of first exposure and date of the last exposure): in the case of rheumatological conditions, similar data will be collected for disease characterization;
3. Selected co-morbidities (cardiovascular disease, systemic infections, cancer and their date of diagnosis);
4. Systemic treatment for psoriasis at entry (drug and dosage) and updates on systemic treatments for psoriasis during follow-up. In case of rheumatological conditions, similar data will be collected on systemic treatment at entry and follow-up;
5. Diagnosis of selected diseases during follow up (date at diagnosis, diagnosed condition with particular attention to infections and cancer)
6. Any relevant suspected adverse event associated with treatment (date of diagnosis, kind of event)
7. Remissions and severe relapse of disease during follow-up

Pooling of individual patient data from national registries

At regular intervals, selected individual patient data will be extracted from national registries and prepared in a standardized form. These data will be included in a centralized database, under the control of the International Coordinating Committee, with appropriate insurance of data confidentiality. Consistency checks of the data will be performed and simple descriptive tables of the data collected will be prepared and circulated among participants after each update.

General issues on analyses and statistical power

Both internal and external comparisons can be made. Internal comparisons will involve analyses of event occurrence in groups defined by different dosages/duration of treatment and/or different drugs. External comparison, to be conducted with caution, will be made by considering incidence rates in selected population samples. For rare events such as cancer incidence, only marked increases of incidence (i.e., twice or more) with respect to the general population could be detected by our system.

In general, the analyses will be split into different steps. A first phase will usually consist of descriptive analyses. A further stage will consider simple univariate analyses. Finally, in-depth analyses centered around specific questions and using more powerful analytical methods, e.g., multivariate models, will be adopted.

Evaluation of the safety profile of systemic agents

Eligible subjects:

All the subjects available in the international database who have received at least one single dose of a prescribed systemic agent for psoriasis or rheumatological conditions in the participating countries will be eligible for the analyses of safety.

Outcome

The primary outcome will be represented by selected adverse events. As far as biological agents are concerned, those of primary interest include: systemic infections, cancer diagnoses, and specific organ involvement or failure (cardiovascular, skin, liver, kidney, musculoskeletal, lung).

Data collection

Diagnoses will be reviewed by an International Safety Review Board. According to the clinical diagnosis, additional information may be required with retrieval of information from medical records, family doctors or directly from the patient.

For the collection of comparative data other sources of information may be considered, including routinely collected data (mortality data, hospital admissions), and Cancer Registries.

Data analysis

Basic descriptive tables presenting numbers of events, ordered by type of disease and therapeutic agent will be prepared at every update of the central database. Rates (standardised by sex and age as appropriate) per 1,000 treated patients will be also computed.

Subsequently, internal comparisons taking into consideration patients receiving different systemic treatments will be conducted. According to the adverse event of interest, various analytical methods may be evaluated. These may include longitudinal analyses of patients' cohorts, nested case-control studies, or case-crossover design (the latter when dealing with acute events and frequent changes of therapies). In any case, the observational nature of the study implies a careful consideration of possible sources of biases and confounding.

Comparisons with data from sources external to the international database may be also considered. In countries/regions covered by cancer registries, standardized incidence ratios for lymphomas and other cancers may be computed (i.e. the ratio between the observed number of cases and the number expected using the sex and age specific incidence data from the cancer registry). In areas not covered by cancer registries the possibility of using national or local estimates of incidence will be investigated.

For severe infections, and other possible events of interest, observed and expected hospitalization rates, using hospital admission data, may be considered. Other data sources for the estimation of expected numbers of events e.g., published and grey literature, *ad hoc* surveys etc. will also be investigated.

Temporal relation between administration and outcome occurrence, dose-response profiles, biologic plausibility, confounding effects of the disease itself, or other treatments, or other potential confounding factors will be evaluated.

International Safety Review Board

The steering committee will appoint an International Safety Review Board that will be in charge of reviewing safety data and will help preparing periodic safety reports. This committee will also be in charge of setting up procedures for the prompt identification and investigation of unexpected alarming events.

Evaluation of the effectiveness of systemic agents for the treatment of psoriasis and prognostic factors

Eligible subjects:

All the subjects available in the overall database with a diagnosis of psoriasis who have received at least one single dose of a prescribed systemic agent for psoriasis in the participating countries will be eligible for effectiveness analysis.

Outcome

Outcome variables will include overall assessment of response to treatment as judged by patient and physician and changes in indicators of severity (e.g., PASI score).

In the long term, simple and cheap outcome measures applicable in all patients seem to be preferable. These may include the number of patients in remission, the number of major disease flare ups, survival within the originally administered therapy, switch to another drug or drug withdrawal because of a lack of response.

Data collection

The centralized database will provide data for the effectiveness analyses. Individual registry data may contain different pieces of information concerning the outcomes of interest. Standardisation will be attempted as much as possible.

Data analyses

An overall description of the outcomes for each systemic agent will be regularly prepared. Data will be initially stratified by age and sex, and then by several other factors as needed.

The analyses will be aimed at:

- comparison of effectiveness between different agents
- overall estimation of short term response rates in a general population setting, as compared to the estimates derived from controlled clinical trials.
- evaluation of the impact of the therapies in groups generally excluded from clinical studies, eg. patients with multiple diseases, older subjects, etc

- identification of prognostic factors for the response to the treatment
- identification of groups of patients at higher risk of non response, complications and adverse events.

The outcome of patients receiving different therapeutic regimens will be compared after adjustment for the most important covariates (eg. age, sex, severity of disease, prior treatments, etc). Univariate and multivariate analyses will be performed, also by means of regression models for longitudinal data, including when needed, time-dependent covariates. Given the observational nature of the study, specific attention will be devoted to the investigation of possible sources of bias and the confounding effect of several variables.

Ethical aspects

The drugs involved are licensed in Europe for the use in psoriasis and are available on the market. All the procedures involved in the different national registries should be part of the usual care of the patients. Patient will be informed that his/her medical records will be anonymously utilised for an international observational study and consent obtained. For the identification of the case report forms only initials and date of birth of the patients will be utilised.

Dissemination of results

Results will be made available to the scientific community and, according to pre-defined criteria, to the general public. Dissemination means may include:

- EU reports
- scientific publications
- presentation of data in a project's website
- collaboration with pharmacovigilance units in different countries and EMEA
- collaboration with patients' organizations.

Annex 2 - Survey of registries of systemic treatments for psoriasis in Europe

	Registry already established?	Coverage of the registry	Systemic treatment considered	Modality of data collection	Support
UK	Yes	Nationwide	Biologicals and Conventional treatments including PUVA	Electronic form	Via professional body BAD Pharmaceutical companies sponsorship
Spain	Yes	Local	Biologicals	Electronic form	Governmental grant pharmaceutical companies sponsorship
Sweden	Yes	Nationwide	Biologicals and Conventional treatments including PUVA	Electronic form	Governmental grant
Italy	Yes	Nationwide	Biologicals and Conventional treatments including PUVA	Electronic form	Governmental grant
Israel	Building a core of an Israeli registry				
Portugal	Waiting for an answer from the Direction of the Portuguese Group of Psoriasis				