PARC-ITP Study

Pediatric and Adult Intercontinental Registry on Chronic ITP

(Worldwide database on chronic ITP
followed by side studies)

STUDY PROTOCOL

version 3.0 of *June 01, 2008*
(including Amendment II)

Intercontinental Childhood ITP Study Group (ICIS)

Cooperating Societies:

European Hematology Association (EHA)

Sociedad Argentina de Hematologia (SAH)

International Society on Thrombosis and Hemostasis (ISTH)

(Other cooperating societies will follow.)

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1. Summary

In 1997 the Intercontinental Childhood ITP Study Group (ICIS) established a Registry ("Registry I"), to promote an international network for the diagnosis and management of acute ITP and in 2001 ICIS published key data of 2035 registered children with ITP (Kühne et al, 2001).

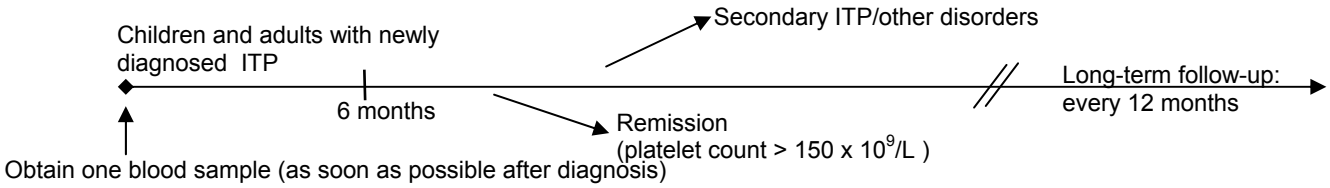
Now a prospective database of both pediatric and adult patients with chronic ITP with long-term follow-up will be established. Since chronic ITP of children and adults shows similarities a common database is warranted to coordinate scientific activities in the field of chronic ITP. EDTA blood samples will be collected for analysis of genome wide single nucleotide polymorphisms (SNPs) in correlation with ITP. Different side studies ("trees in the park") may follow as modules on the basis of the PARC-ITP study.

Hypothesis
ITP is a heterogeneous disorder. Genetic variants play a role in the pathogenesis or perpetuation of ITP. Specific SNPs may be useful markers of susceptibility, severity, chronicity and responses to therapy in patients with chronic ITP.

Study end points
1 Demographic data of children and adults with ITP
2 Natural history by long-term follow-up data every 12 months (lifelong)
3 Validity of diagnosis: i.e. similarities and differences in various age groups
4 Analysis of genome wide SNPs in correlation with ITP

Eligibility
Children and adults with newly diagnosed ITP.
Informed consent and IRB approval is required before study entry.

Design
Worldwide cooperation of investigators willing to register patients anonymously. Data collection by registry process. Collection of one EDTA blood sample of min. 3-5 ml per patient and if possible an age and gender matched 'healthy' control. **Blood sampling is voluntary and does not exclude from study participation.**



Questionnaires
Initial, 6-month, 12-month, yearly forms
2 page questionnaire, mailing coordinated by ICIS, central data office

Analysis and Publication
An interim analysis of demographic and clinical data will be performed when 1'000 eligible patients are enrolled or no later than 5 years. An interim analysis of genome wide SNPs will be performed when 500 blood samples from ITP patients have been collected or no later than 5 years. Investigators will be announced by accurate list on the website http://www.itpbasel.ch (see also ICIS Publication Policy).

2. Background

Idiopathic thrombocytopenic purpura (ITP) is a disorder in which the production of (auto)antibodies to the patient's own platelet proteins results in premature platelet destruction in the peripheral circulation resulting in thrombocytopenia (Provan D 2003, Kühne T 2003, Blanchette V 2003). Hemorrhagic complications and the degree of thrombocytopenia do not particularly well correlate. Clinical and laboratory similarities and differences among children and adults are not well defined.

Genetic studies of autoimmune disorders including rheumatoid arthritis and diabetes mellitus have shown that natural polymorphic variants of genes encoding immune response proteins play a major role in disease susceptibility and severity. We wish to apply a similar strategy to ITP by analyzing polymorphic markers in a variety of genes encoding cytokines, their receptors and other immunoregulatory genes, in order to determine whether these influence the natural history of ITP i.e. outcome, the site of platelet destruction, platelet survival and response to treatments in current use (Foster 2001). The assessment of genetic markers in a disorder such as ITP may help predict which ITP patients are at risk of suffering chronic relapsing ITP, those likely to have severe ITP and finally, the likelihood of response to treatment.

2.1 Pathogenesis of Chronic ITP

The cause of ITP is not known. The pathophysiology is autoimmune (Harrington 1951), autoantibodies and their related antigen epitopes are well described (McMillan 2003), as well as the disturbed T-cell responses (Semple 2003). There are many debated different mechanisms.

2.2 Classification of ITP

ITP may be divided into

- an acute and a chronic form based on the duration of the disease
- a pediatric and an adult form
- a symptomatic and an asymptomatic disease
- a primary and a secondary form

2.3 Management of ITP

Practice guidelines have been established (Eden 1992, George 1996, UK Guideline 2003) but not strictly followed (Bolton-Maggs 1997 and Vesely 2000). Management of ITP is divided into measures to prevent hemorrhagic complications.
In children and adults with symptomatic ITP the treatment goals are not well established. There have been few trials comparing different treatments in chronic ITP but it is recognized that response varies greatly to different treatments.

2.4 Patient number

The registry will accrue as many patients as possible. The sample size analysis will not be performed based on the aims of the study mentioned in 3.1. to 3.4.

2.5 Hypothesis

ITP is a heterogeneous disorder. Genetic variants play a role in the pathogenesis or perpetuation of ITP. Specific SNPs may be useful markers of susceptibility, severity, chronicity and responses to therapy in patients with chronic ITP.

3. Aims of study

The objectives of this multicenter international registry study (also called PARC-ITP study) are as follows:

Primary objective:

3.1 To establish a database on children and adults with ITP (demographics), to analyse the heterogeneity of ITP and to identify new patient selection criteria for future trials.

Secondary objectives:

3.2 To study the natural history of ITP based on a long-term follow-up study

3.3 To validate the diagnosis

3.4 To analyze genome wide SNPs in correlation with ITP

4. Brief outline of project

Adult and pediatric patients will be those attending the haematology clinics at participating centres. Patients will undergo local ITP workup in order to exclude underlying diseases that are known to cause thrombocytopenia e.g. systemic lupus. Patients who have no evidence of underlying disease and in whom the thrombocytopenia is idiopathic will be invited to take part in the project.

5. Inclusion criteria and study endpoints

5.1 Patients

Inclusion criteria of ITP patients

- Children from the age of 2 months and above with newly diagnosed ITP
- Adults with newly diagnosed ITP

Participating patients are considered 'newly diagnosed' at first presentation with platelet counts < 150 x 10^9/L and assumption of ITP by the treating physician.

Exclusion criteria of ITP patients

There are no exclusion criteria

5.2 Controls

Inclusion criteria for blood donors/patients serving as 'healthy' controls

Patients undergoing anaesthesia or surgery for trauma, circumcision, tonsillectomy/adenectomy or other surgery, without a history of chronic disorder/s, will be invited to serve as controls (age and gender matched) and to provide one blood sample of min. 3-5 ml.

5.3 Primary end points

5.3.1 Demographic data of children and adults with ITP

5.3.2 Follow up data after 6 months duration of ITP, after 1 year and from then on yearly concerning
- Bleeding symptoms
- Platelet counts
- Management

5.3.3 Validation of diagnosis

5.3.4 Analyses of genome wide SNPs in correlation with ITP

5.3.5 Database for related studies

6. Completing Form and Procedure

6.1 Written approval of this study by the local Ethics Committee or Institutional Review Board (IRB) of each participating center and informed consent of ITP patients and patients serving as controls will be required before the data can be submitted (see Forms E for adults and I for controls).

6.2 Patients will be enrolled from participating centers whose investigators agree in writing to attempt to register all new patients with ITP (see attached "Investigator's Participation form") and to obtain one EDTA blood sample (min. 3 ml) of the ITP patient and, if possible, a control. **Blood sampling is voluntary and does not exclude from study participation.**

6.3 **Initial form**
The initial form will collect data on each patient anonymously and the name and address of each participating investigator/institution.

6.4 **Follow-up form**
The follow-up form will be sent to each investigator at relevant time points (after 6 months, 12 months, and then yearly) by the central data office.

6.5 **Controls**
An attempt will be made by the investigators to obtain one EDTA blood sample (min. 3-5 ml) from 'healthy' controls, if possible age and gender matched.
On Form H the following data will be collected in controls: age, gender, ethnical background, reason for surgery and anamnestic exclusion of a chronic disorder (cancer, diabetes mellitus, arterial hypertension, inherited disorders, autoimmune disorders). **Please fax Form H to +41 61 685 65 66 and then enclose both forms H and K when shipping the blood sample(s).**

6.6 **Data submission**
Data are to be submitted online to www.parc-itp.net (or by fax) ~~or by regular mail~~ to the central data office.

6.7 **Referral patients**
In cases where a prospective collection of data is not possible, i.e. if your center sees mainly referred patients, data may be submitted retrospectively for up to 18 months after initial diagnosis of ITP.

7. Blood sampling

7.1 **Blood sampling is voluntary and does not exclude from study participation.**
Drawing blood will be part of a routine peripheral venipuncture during initial evaluation of ITP patients or, for patients serving as controls, during preparation for anaesthesia or surgery, thus there is no need for venipuncture solely for the study.

7.2 One EDTA blood sample of min. 3-5 ml per 'healthy' control and patient will be drawn, for the latter preferably at the time of diagnosis or as soon as possible.

7.3 **Labels for the EDTA blood sample** are provided by ICIS central data office. Blood samples must be labelled as ICIS blood sample, with Unique Patient Number (UPN),

assigned by the participating center and matching the number entered to the online PARC-ITP database, and with the participating Institution/Investigator.

Intercontinental Childhood ITP Study Group (ICIS) UPN: Institution/Investigator:

7.4 Freeze the EDTA blood sample immediately after drawing and store locally at min. –20°C.
Ship in batches of min. 10 samples or every 3 months, at room temperature, and enclose Form H (questionnaire for controls) and Form K (shipping form).

7.5 An express courier service will be organized and paid for by ICIS central data office.

Shipping address for blood samples:

University Children's Hospital Basel UKBB Laboratory of Hematology **PARC-ITP** Spitalstrasse 33 CH-4056 Basel, Switzerland

8. Ethical Considerations

8.1 The declaration of Helsinki and its subsequent amendments shall be the accepted basis for the ethical conduct of the clinical investigation.
The protocol has been approved by the Intercontinental Childhood ITP Study Group, and will be approved by the local, regional or national ethical committees/institutional review boards of each participating institution. All changes to the protocol must be reviewed and approved prior to implementation.

8.2 **Informed consent, patient anonymity and data protection**
Registrations will be accepted only of ITP patients and controls of whom there is informed consent. Personal identifiers of ITP patients and controls will not appear within the database; instead a unique patient number will be allocated to the patients. The online PARC-ITP database is password protected and data is safeguarded with SSL 128MB encryption.

8.3 **Privacy of ITP patients and controls**
Results of genetic analysis will not be handed back to the participating investigators, thus there is no potential risk of loss of privacy. Individual patient data will not be published.

9. Study Administration

9.1 **Central Data Office**
All study administrative procedures are coordinated and conducted by the ICIS

central data office in Basel, Switzerland. These include collection of registration forms, data collection and management, call for follow-up data.

9.2 **Participating Centers**
A participating center can be any institution with expertise in the diagnosis and management of patients with ITP.

9.3 **List of participating investigators** and centers will be published at www.itpbasel.ch

9.4 **Patient recruitment**
Every patient with newly diagnosed ITP will be contacted by the treating physician. An informed consent will be obtained.

9.5 **Publication procedures**
An interim analysis of clinical data will be performed when 1'000 eligible patients are enrolled or no later than 5 years. An interims analysis of genome wide SNPs in correlation to ITP will be performed after collection of the first 500 blood samples, or not later than 5 years. A writing committee will be established, consisting of members of ICIS, EHA and other organizations. A core committee of these will be responsible for a publication in regard to each journal's publication policy.

9.6 Further societies and individuals will be contacted to become cooperative participants of the study.

9.7 Reimbursement of centers
Shipping of EDTA blood samples will be paid for by the ICIS central data office.

10. Sponsor

The Intercontinental Childhood ITP Study Group (ICIS) serves as sponsor for this project. This non-profit organization was founded in 1997 by Paul Imbach (principal investigator) and Thomas Kühne (secretary). The following persons are currently ICIS Board members (February 2004): F Bessho (Japan), PHB Bolton-Maggs (UK), V Blanchette (Canada), G Buchanan (USA), H Donato (Argentina), P Downie (Australia), M Elalfy (Egypt), R Kohan (Argentina), J Lusher (USA), M Marks (Australia), B Saxon (Australia), A Shirahata (Japan), J Wu (Canada), S Zimmerman (USA).

The itpfoundation (see www.itpfoundation.org) supports the pediatric part of the PARC-ITP study. Fundraising will be continued by ICIS.

11. References

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12. Appendices: Forms/Questionnaires

You will find these documents on our homepage: www.itpbasel.ch

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