Prediction of the clinical course of immune thrombocytopenia in children by platelet kinetics

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Abstract

Introduction: Childhood immune thrombocytopenia (ITP) is a rare autoimmune disorder characterized by isolated thrombocytopenia. Prolonged ITP (persistent and chronic) leads to a reduced quality of life for children in many domains. To provide optimal support for children, with ITP, it is important to be able to predict those who will develop prolonged ITP. This study aimed to develop a mathematical model based on platelet recovery that allows the early prediction of prolonged ITP. Methods: In this retrospective study, we used platelet counts from the six months following the diagnosis of ITP to model the kinetics of platelet evolution using a pharmacokinetic-pharmacodynamic model. Results: In a learning set (n=103), platelet counts were satisfactorily described by our kinetic model. The $K_{heal}$ parameter, which describes spontaneous platelet recovery, allowed a distinction between acute and prolonged ITP with an AUC of 0.74. In a validation set (n=58), spontaneous platelet recovery was robustly predicted using platelet counts from 15 (AUC=0.76) or 30 (AUC=0.82) days after ITP diagnosis. Discussion: In our model, platelet recovery quantified using the $k_{heal}$ parameter allowed prediction of the clinical course of ITP. Future prospective studies are needed to improve the predictivity of this model, in particular, by combining it with the predictive scores previously reported in the literature.

INTRODUCTION

Childhood immune thrombocytopenia (ITP) is a rare hematological disorder that occurs in approximately 5 to 10 children per 100,000 (1). It is an acquired autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count < 100 x 10^9/L) caused by increased platelet destruction, alterations in cellular immunity, and impaired platelet production (2). ITP is a heterogeneous disease that shows variable etiology, bleeding symptoms, need for treatment, response to therapy, and duration (3). There are several different types of ITP evolution in children: (i) acute ITP, newly diagnosed within the last three months, (ii) persistent ITP, which covers a period between 3 and 12 months after diagnosis, and (iii) chronic ITP, with more than 12 months of evolution.

The evolution of ITP is difficult to predict. Generally, the longer it persists, the heavier the disease burden for the children and their families. On a daily basis, ITP leads to a reduced quality of life of children in
many domains, especially for persistent and chronic ITP (5). For example, severe daily fatigue is reported by children with chronic ITP (6-7). Chronic ITP also affects children’s social lives, with restrictions on certain physical activities and absenteeism from school to attend medical appointments or have blood tests (8-9). At the psychological level, chronic ITP is associated with increased levels of stress, anxiety, depression, and isolation in children (10).

In an effort to provide optimal support to children and their families, a number of studies have examined the factors associated with the clinical course of ITP. Among the many clinical predictors studied, being female, being older, and having had an insidious onset of the disease, without infectious or vaccinal triggers, have been associated with chronic ITP (11).

Among the biological factors tested, only the presence of antinuclear antibodies and the platelet count at diagnosis have been shown to be associated with the clinical course of ITP (11). At diagnosis, low thrombocytopenia (> 20x10^9/L) is also associated with a risk of chronic ITP (11), whereas stronger thrombocytopenia (< 5x10^9/L) is associated with a low risk of chronicity (12). Further, Schmidt et al. developed a score which gathered these factors into a recovery score displaying good performance to predict a prolonged disease for a given patient (13). However, their model does not account for platelet evolution over time. To date, few studies have precisely investigated the evolution of platelet count kinetics and the risk of chronicity of ITP. Choi et al. found that patients with chronic ITP had significantly lower platelet counts one and three months after diagnosis than patients with acute ITP (14). On the contrary, Higashide et al. found no association between ITP progression and platelet counts at 12 months (15).

In this context, we aimed to develop a mathematical model based on platelet kinetics that allows the early prediction of ITP persistence or chronicity.

2. METHODS

2.1 Data Collection

2.1.1. Patient population

This retrospective observational study was carried out using data from the medical records of patients under 18 years of age followed for ITP in five French hospitals (Tours, Orléans, Nantes, Angers, Rennes). The diagnosis of ITP was made according to the 2009 international recommendations (16). It is a diagnosis of elimination made when there is a combination of clinical hemorrhagic syndrome (purpura, mucosal, or visceral hemorrhage) and isolated peripheral thrombocytopenia [?] 100 x 10^9/L. Thrombocytopenia should not be associated with other types of cytopenia, immune deficiency, or coagulation disorders. The presence of purpura should not be secondary to hematological malignancy, cancer, alloimmunization or, medication. A relapse is characterized by the recurrence of thrombocytopenia [?] 100 x 10^9/L, with or without a clinical bleeding syndrome (16). ITP was considered to be acute when the thrombocytopenia improved within three months, persistent when the recovery from thrombocytopenia took between 3 and 12 months, and chronic when thrombocytopenia persisted beyond 12 months (16). Prolonged ITP was considered to be the association of persistent and chronic ITP. This study was approved by the health data club of the Tours Hospitals (F20200907070428) and by the clinical research assistance ethics group (#2020 076).

2.1.2. Enrolment criteria

Patients aged 0-18 years with ITP followed at the participating hospitals were assessed. Secondary ITP or ITP with associated hematological or extra-hematological syndromes (hematological malignancy, acquired or primary immuno deficiency, genetic syndrome, systemic lupus erythematosus) were excluded. Patients who received a consultation or hospitalization related to ITP but whose follow-up was carried out in another center and those with missing data (less than five platelet counts within the first 90 days) were not assessed.

2.1.3. Data collection

The following clinical data were collected from the patient medical records: age at diagnosis, gender, sex, Buchanan score (17), acute or insidious presentation (bleeding symptoms for more than 14 days before
diagnosis), and recent infections or vaccination within 21 days prior to the diagnosis of ITP. The treatment received and the dates of administration, as well as other medical treatment, during the first six months were recorded. Patients in the study were treated in the acute phase according to French recommendations: in the presence of thrombocytopenia < 10 x 10^9/L or a bleeding syndrome with a Buchanan score ≥ 3, treatment consisted of polyvalent immunoglobulin (0.8-1g/kg) or 4 mg/kg/day of prednisolone/prednisone. Biological data collected consisted of the platelet and leukocyte counts at diagnosis, evolution of platelet counts in the first six months, immunoglobulin G levels, and the presence of anti-nucleus antibodies.

2.2. Statistical analysis

2.2.1. Population kinetic modeling of platelet counts

The aim of this study was to provide an early prediction of disease progression, i.e., prolonged (persistent/chronic) versus acute ITP. Platelet recovery following treatment was assessed using a kinetic model that was built, validated and which predictive performance was challenged in an external validation dataset. This model, derived from pharmacokinetic and pharmacokinetic-pharmacodynamic (PK-PD) models (18; 19) allowed a description of the platelet count over time and is presented in detail in Supporting Information Material. Briefly, the model described the influence of treatment on platelet count turnover and included a parameter (k_heal) that describes spontaneous platelet recovery and, thus, ITP improvement. Initial application of the model showed that this value was 70-fold lower in persistent/chronic than acute disease (p = 0.0022, Supporting Information Material). This motivated us to investigate the potential use of the k_heal value estimated for each patient as an early predictor of the possible evolution towards persistence/chronicity.

2.2.2. Data splitting

To ensure the predictive performance of a model, different datasets must be used to estimate the kinetic parameters (learning phase) and evaluate model-predicted disease evolution (validation phase). Thus, learning and validation subsets were made using the data for patients from three (Tours, Orleans, and Nantes) and two centers (Angers and Rennes), respectively. We evaluated the predictive performance of the model by evaluating the full validation subset (Vfull), as well as two subsets for which the validation subset consisted of platelet counts truncated to 30 (TV30) or 15 (TV15) days.

2.2.3. Model development

Kinetic model parameters were estimated by nonlinear mixed-effect modeling (20) (population approach) using Monolix Suite 2019 (Lixoft(r), Antony, France). With this approach, widely used in pharmacology, data from patients of a given population are simultaneously computed to estimate the interindividual distribution of kinetic parameters. This interindividual distribution allows quantification of: (i) the mean (typical) value of each parameter, (ii) interindividual variability (interindividual variance), (iii) the influence of individual sources on such variability (covariates), and (iv) the estimated parameter values for each patient.

The learning subset was used for the development of our platelet kinetic model and to estimate the interindividual distribution of the kinetic parameters and then individual parameter values. Individual k_heal estimates of patients from the learning subset were used to determine a threshold value for which a k_heal below or above this threshold is predictive of persistent/chronic or acute disease, respectively. The value of the k_heal threshold was determined using receiver-operating characteristic (ROC) analysis, with respect to the actual diagnosis, by minimizing the Youden index (defined as Y = sensitivity + specificity – 1).

2.2.4. Evaluation of the predictive performance of the model

These distributions were then applied to truncated validation subsets TV30 and TV15 to estimate the respective individual kinetic parameter values. Then individual k_heal estimates from Vfull, TV30, and TV15 were tested to predict disease evolution. These estimates were compared to the threshold value determined in the learning subset: patients with k_heal estimates below or above the threshold were inferred as acute or persistent/chronic ITP. Finally, these inferences were compared to the actual diagnosis by calculating the
sensitivity (Se), specificity (Sp), positive (PPV) and negative (NPV) predictive values, and Cohen’s kappa (Ka).

RESULTS

Patient selection and characterization

We identified 231 patients who consulted for ITP at the study hospitals. Eighteen patients were excluded because they did not have isolated ITP and 52 were excluded because of a lack of data, follow-up in another hospital, or a halt in treatment (Fig. 1). Finally, 161 patients were included in our study, allowing us to constitute a learning cohort of 103 patients and an external validation cohort of 58 patients (Table 1). The learning cohort consisted of 68 patients with acute ITP, 11 with persistent ITP, and 24 with chronic ITP. The external validation cohort consisted of 35 patients with acute ITP, three with persistent ITP, and 20 with chronic ITP. No significant difference was found between the various clinical and biological characteristics of these two cohorts (Table 1).

Prediction of ITP evolution

From the learning set, platelet counts were satisfactorily described by our kinetic model and the kinetic parameters were accurately estimated (Supporting Information Material 2). Notably, the mean $k_{\text{heal}}$ value was 0.0012 day$^{-1}$, with very high interindividual variability (290%); such variability was responsible for most of the variability of the platelet count data over time (Supporting Information Material). ROC analysis showed a threshold value of $k_{\text{heal}} = 0.00743$ days; patients with a $k_{\text{heal}}$ below this value were declared to have persistent/chronic disease, with a Se of 0.72, Sp of 0.66, a PPV of 0.53, a NPV of 0.81, and Ka of 0.68 (Table 2).

Use of the interindividual distribution of the kinetic parameters and threshold determined in the learning set on the validation set yielded similar values (Se = 0.70, Sp = 0.75, PPV = 0.64, NPV = 0.79, Ka = 0.73) (Table 2). These values remained similar using validation sets with platelet counts truncated to 30 and 15 days, except for Se, which was lower for 15 days (0.57, Table 2). The $k_{\text{heal}}$ value was not associated with the clinical-biological characteristics of the children with ITP in either the learning or validation sets.

DISCUSSION

We report a mathematical model that describes the evolution of platelet counts over time and allows early prediction of prolonged ITP in children.

Early prediction of prolonged ITP was already reported in previous works. Notably, demographic (age, sex), clinical (disease onset, preceding infection or vaccination), or biological (platelet counts at diagnosis) were already reported to be not only associated with (11), but also predictive of prolonged disease (13). Besides, previous publications used linear regression to describe platelet count evolution over time but reported conflicting results, this evolution being related (14) or not (15) with disease evolution.

In this work we report the first kinetic model quantifying the kinetics of platelet count over time in ITP children. This model is made of a differential equation system describing platelet turnover and accounts for the disease onset and evolution, and of treatment. Model parameters were estimated nonlinear mixed-effect modelling (population approach). Population approach has been extensively used to describe pharmacokinetic and pharmacokinetic-pharmacodynamic (PK-PD) relationship of drugs, biomarker kinetics (21; 22) and tumor growth (23) over time. Notably, this approach was used to describe the kinetics of blood cell lines after myeloablative chemotherapy (18). One of the main advantages of population modelling is that it does not require a large number of subjects. The increase in the use of population kinetic modeling may open the way to the modelling of complex phenomenons, such as the response to treatment or prediction of the clinical course.

Interestingly, our model allows quantifying the natural disease recovery by the parameter $k_{\text{heal}}$, which present a very large interindividual variability. This value may be interpreted as the natural recovery if no treatment is administered: platelet recovery is slower in patients with a lower $k_{\text{heal}}$ value. Being a first-order rate
constant, a half-life of recovery may be derived by calculating $T_{1/2} = \ln(2)/k_{heal} = 1.6$ years in mean in the learning cohort. Early attempts showed that $k_{heal}$ is strongly associated with prolonged disease ($p = 1.02 \times 10^{-8}$, Supporting Information Material). Half-life of recovery was therefore 6 months and 35 years in acute and prolonged PTI patients, respectively. However, this value should be considered with caution since was estimated from treated patients.

Our model showed good performance in early discrimination between acute vs. prolonged ITP starting from 15 days after diagnosis. The predictive performance of our model is similar to the clinical score developed by Schmidt et al, with comparable ROC AUC of approximately 0.70 (13). Furthermore, our approach is complementary to the score developed by Schmidt et al.; our approaches may be gathered in a model that would further improve the prediction of prolonged disease.

Nevertheless, we were neither able to detect an association of $k_{heal}$ with demographic, clinical or biological characteristics, nor discriminate persistent vs. chronic ITP. This may be due to the fact that our model was developed in retrospective observational data, as in most of previous studies.

Such data are dependent on the time of recovery of patients and the monitoring habits of each center, which may have induced a bias in the estimation of the model parameters (including platelet recovery). Future prospective studies in which all patients are monitored in the same way (same number of platelet counts), regardless of the treatment or evolution of ITP, will be necessary. This would allow us to refine the model parameters and to be able to discriminate between persistent and chronic ITP.

Anticipating the evolution of the disease at the individual level would make it possible to provide more precise information that will enable them to participate in the therapeutic strategy or monitoring of children with ITP. Our innovative new approach will do this by enabling early detection of the clinical course of ITP in children.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

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REFERENCES


LEGENDS

Table 1
ITP: Immune Thrombocytopenia

Table 2
PPV: positive predictive value, NPV: negative predictive value, AUC: area under the receiver operative characteristic (ROC) curve, TV: validation subset truncated of platelet counts 30 or 15 days after diagnosis

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