Bourse de mobilité à l'étranger 2019-2020

Association ADICARE

PRENOM ET NOM DU LAUREAT : GUILLAUME COUTANCE

PRENOM ET NOM DU RESPONSABLE DU PROJET (DU LABORATOIRE D'ACCUEIL) :

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PRENOM ET NOM DU RESPONSABLE DU LABORATOIRE D'ORIGINE :

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TITRE DU PROJET :

Création d'un outil intégratif de stratification individuelle du risque de rejet humoral cardiaque

A. Contexte de la mobilité

Cardiologue spécialisée en transplantation cardiaque à la Pitié-Salpêtrière, cette mobilité aux États-Unis, dans le service réalisant le plus grand nombre de transplantations cardiaques chaque année dans le monde, s'inscrit dans le cadre d'un projet de carrière hospitalo-universitaire. Au cours de cette mobilité, j'ai pu m'intégrer efficacement aussi bien à l'équipe de recherche clinique qu'à l'équipe clinique du fait de ma participation aux staffs réguliers du service. En parallèle du projet initial, j'ai pu travailler sur deux autres projets : i) analyse des résultats d'un essai thérapeutique prospectif évaluant l'inhibition du complément comme stratégie thérapeutique des patients à haut risque immunologique et comparaison à un groupe contrôle issu de notre cohorte de patients de la Pitié-Salpêtrière présentant un risque immunologique équivalent (**Annexe 1**, *American Journal of Transplantation*, in press, 2ème auteur) et ii) rédaction d'un chapitre concernant les stratégies d'immunomodulation en transplantation thoracique pour le livre de référence de l'International Society of Heart and Lung Transplantation (**Annexe 2**, premier auteur).

B. Rappel synthétique des objectifs initiaux du projet

B.1. Intérêt général

Le dépistage et le diagnostic du rejet humoral cardiaque reposent sur la réalisation de biopsies endomyocardiques (BEM) itératives. L'absence d'outil de stratification individuelle du risque de rejet impose la réalisation de nombreuses BEM selon un protocole commun à tous les patients, les exposant ainsi aux risques de cet examen invasif alors même que l'incidence du rejet à l'échelle de la population est faible.

B.2. Objectifs scientifiques

Notre objectif était de développer et de valider un outil intégratif permettant de stratifier le risque individuel de rejet humoral afin d'adapter le suivi par BEM au risque individuel de rejet (médecine personnalisée). Nous souhaitons appliquer des modèles statistiques permettant l'évaluation de la probabilité de rejet à l'échelle de chaque biopsie. L'idée sous-jacente étant de limiter le recours aux biopsies si la probabilité pré-test est considérée comme faible.

C. Méthodologie synthétique

En plus des statistiques descriptives usuelles, nous avons appliqué un modèle de régression logistique mixte, modèle adapté à l'analyse des données longitudinales (chaque patient ayant de multiples résultats de biopsies au cours de la première année) et permettant l'obtention d'une probabilité individuelle, à l'échelle de chaque biopsie.

D. Résultats préliminaires : abstract soumis pour le prochain congrès de l'ISHLT

Derivation and validation of an individual risk score of biopsy-proven antibody-mediated rejection after heart transplantation: a population-based study.

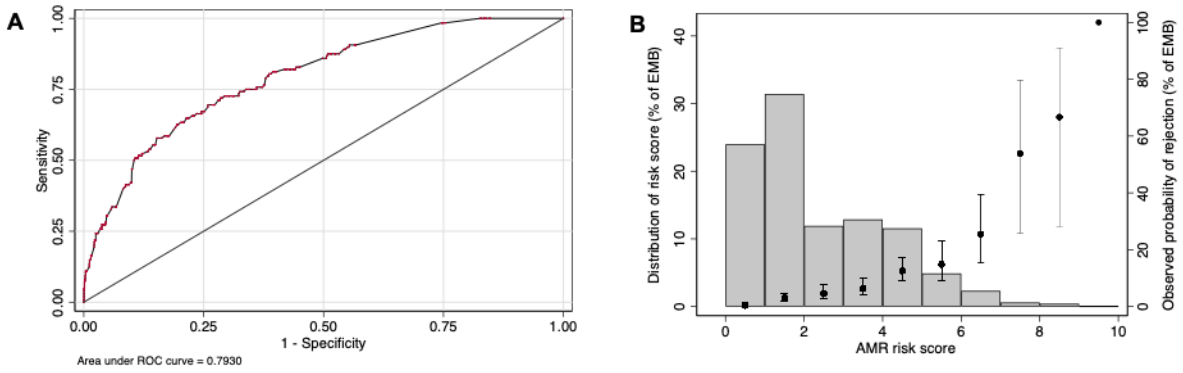
Background
Routine endomyocardial biopsies (EMB) remain the gold-standard for the monitoring of antibody-mediated rejection. Identification of risk factors for AMR could improve individual risk stratification and limit the number of routine EMB.

Methods
In this retrospective single center study, consecutive patients transplanted between 2012 and 2017 (n=700) were randomly distributed between a training (2/3, n=463) and a test (1/3, n=237) set. We applied mixed effect logistic regression with a random intercept to identify independent predictive variables associated with biopsy-proven AMR at the level of each EMB. An AMR risk score was derived by applying the β-coefficients attributed to each predictive variable.

Results
A total of 6,403 EMB from 700 patients were analyzed. AMR pAMR1(I+), pAMR1(H+) and pAMR ≥2 were diagnosed on 162 (2.5%), 152 (2.4%) and 98 (1.5%) EMB. In the derivation cohort, we identified 5 independent variables associated with AMR: time post-transplant ($p<0.001$), pre-transplant sensitizing event ($p=0.003$), circulating donor-specific antibody at the time of EMB ($p=0.010$), left ventricular dysfunction ($p=0.018$) and prior history of pAMR2 ($p<0.001$). The area under the ROC curve was 0.801 in the test set (Figure 1A). We observed a stepwise increase in the risk of rejection with increasing AMR risk score (Figure 1B).

Conclusion
We identified 5 independent predictive variables associated with AMR and derived an AMR risk score. Avoiding EMB at low risk might spare numerous EMB while missing a limited number of AMR.

Validation cohort



E. Discussions et perspectives

Nous complétons actuellement notre base de données de la Pitié afin de pouvoir réaliser une validation externe de ce score avant soumission de nos travaux.
Une fois ce score validé, nous souhaitons l'intégrer dans une stratégie plus large de stratification du risque de rejet humoral, qui inclurait non seulement une stratification clinique du risque du rejet, mais aussi une composante biologique par le dosage d'ADN libre circulant du donneur dans le sérum du receveur. Ce projet devrait débuter dans le service de greffe de la Pitié-Salpêtrière avant la fin de d'année.

ANNEXE 1. Eculizumab for heart transplantation at high immunological risk. *AJT*, in press.

Background. Highly sensitized heart transplant candidates have a higher waitlist mortality due to a longer wait time to transplant as a result of a highly restricted suitable donor pool. Complement activation is a major mechanism of antibody-mediated injury to the allograft. Its inhibition at the time of transplant might allow transplant against donor specific antibodies (DSA), thereby broaden the donor pool of these high-risk patients, while minimizing allograft injuries. We conducted a prospective pilot study aimed at evaluating the efficacy of the complement inhibitor eculizumab at transplant in highly sensitized candidates. **Methods.** We performed a single-center, single-arm, open-label trial. Patients with panel reactive antibodies (PRA) ≥ 70% at any time before transplantation and transplanted with pre-formed DSA were eligible to enter the study. In addition to cytolytic induction therapy and polyvalent immunoglobulins, patients received 9 infusions of eculizumab during the first two months post-transplant (total dose = 9,300 mg). The primary composite endpoint was the incidence of biopsy-proven antibody-mediated rejection (AMR) ≥ pAMR2 and/or left ventricular dysfunction at one year. Secondary endpoints included hemodynamic compromise, allograft rejection, patient survival, development of cardiac allograft vasculopathy (CAV) and evolution of mean fluorescence intensity (MFI) DSA during the first year. A pre-specified analysis was performed comparing eculizumab-treated patients to a matched cohort of patients treated with cytolytic induction, plasmapheresis and polyvalent immunoglobulins at the time of transplant (nearest neighbor propensity matching). **Results.** A total of 20 patients were included. They were mostly women (n = 16, 80%) with a prior history of sensitizing event (n = 18, 90%) including 5 redo heart transplantations (25%). Median cPRA and MFI of immunodominant DSA at transplant were 95% (90-97%) and 6,250 (5,000-10,000), respectively. Positive retrospective B-cell (median=264, IQR=220-310) and T-cell (median=102, IQR=81-201) flow crossmatches were found in 14 and 11 patients, respectively. The primary endpoint occurred in 4 patients (20%) and was only driven by biopsy-proven AMR. Overall survival at 1-year was 90%. No death was adjudicated as resulting from antibody-mediated graft injury. One patient was diagnosed with CAV progression. When comparing to matched control patients, we observed a dramatic reduction in the incidence of biopsy-proven AMR in patients treated with eculizumab (HR=0.36, 95%CI=0.14-0.95, p=0.032). **Conclusions.** Our findings support the use of a complement inhibition-based strategy for heart transplantation at high immunological risk.

ANNEXE 2. Current Strategies in Immune Modulation and Desensitization Protocols.

Pre and post-transplant impact of allosensitization. Allosensitization represents a major barrier to thoracic organ transplantation (HTx). The presence of pre-transplant antibodies to Human Leucocyte Antigens (HLA) is associated with limited access to transplantation as emphasized by an increased waiting time and mortality on the list, even in case of prioritization of highly sensitized candidates.[4] High calculated panel reactive antibody (cPRA) and the presence of pre-formed donor-specific antibodies have been associated with acute allograft rejection, development of cardiac allograft vasculopathy (CAV) and mortality after heart transplantation. **Desensitization therapies.** In order to broaden the donor pool and offer highly sensitized candidates a decent chance to be transplanted, different protocols aimed at decreasing the number and the strength of anti-HLA antibodies have been reported during the last decade. Despite the absence of new immunosuppressive therapy in the field of solid organ transplantation, new opportunities in the prevention and treatment of allosensitization are offered by the continuous progress in the management of hematologic malignancies and autoimmune disorders. Their FDA-approved therapies, mostly monoclonal antibodies, may indeed be useful in the management of sensitized candidates since these conditions share common pathophysiological pathways with allosensitization and antibody-mediated rejection (B-cells/plasma-cells, antibody binding, complement activation, cytokine production…). Importantly, the desensitization protocols that will be further discussed in this chapter are mostly based on off-label use of therapies that are FDA-approved in other clinical settings. **Chapter overview.** In this chapter, after a brief summarize of the pathophysiology of the humoral response in order to better understand the mechanism of action of desensitization therapies, we will review the evolution of antibody testing in the field of solid organ transplantation. Then, we will detail the rational for use, approved indications, experimental and clinical studies (both in kidney and thoracic organ transplantation), toxicities and practical use for each desensitization therapy. Finally, we will discuss a practical clinical approach to the issue of allosensitization in heart transplant candidates.