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Novel data-driven stochastic model for antibody dynamics in kidney transplantation ⋆

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Abstract: Falls in the serum levels of donor specific HLA antibodies (DSA) after kidney transplantation are of great clinical interest, as they are associated with resolution of rejection and good long term outcomes in patients at high risk of graft loss. A data-driven model in the form of third order differential equation has been developed to describe the dynamics of the falls in DSA after renal transplantation. The model characterises the post transplant DSA behaviour for two groups of renal transplant recipients: those who experienced acute antibody mediated rejection (AMR) in the first days after operation and those who did not. A variational Bayesian inference method was employed to find the form of the model, infer the system parameters and extract the information of the recognisable patterns and the common features in DSA post transplant dynamics. Three models of different order have been investigated, and the third order linear model with four parameters outperformed the models of lower orders. The inferred deterministic parameters were found to be significantly different between the two groups of people with and without AMR. The eigenvalues for each DSA time series have been calculated and compared between the groups. A higher frequency of oscillation and a faster dissipation rate of antibodies have been found in the AMR group, which demonstrate a potential for intelligent laboratory interrogation of the underlying immunological mechanisms, which at present are entirely opaque.

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1. INTRODUCTION

Kidney transplantation is commonly performed despite human leukocyte antigen (HLA) incompatibilities between the donor and the recipient. HLA defines the immunological character of each of us, and there are many different HLA types that allow for inter-individual variation in the immune response, likely to confer a survival benefit to the species. Differences between donor and recipient HLA drive an immune response (called rejection) against the graft. The portion of this response driven by T lymphocytes has effectively been managed by improvements in drug therapy over the last 55 years. However, some individuals also develop an antibody response. This antibody response to non-self HLA can be produced by pregnancy and blood transfusion as well as organ transplantation; can persist for life; can cause severe rejection and graft loss. Mechanisms underlying the control of antibody production are poorly understood, and treatments given to patients with HLA antibody mediated rejection (AMR) are often ineffective. In recent years, the development of a microbead assay using purified HLA protein has made the identification and quantification of different types of DSA in patient sera possible, as explained in Thaunat et al. (2009). High titres of preformed DSA have been recognised as the cause of acute AMR since strong evidence was provided by Patel and Terasaki (1969). Therefore, removal of the existing DSA before transplantation through plasmapheresis has been widely applied in practice for desensitisation and prevent acute AMR, as explained in Krishnan et al. (2013) and Terasaki and Cai (2008). But the relationship between DSA and chronic rejection is still not clear, as various factors are involved (see review Nankivell and Chapman (2006)). In recent years, a number of publications such as Sellarés et al. (2012), Terasaki and Cai (2008), Zachary and Leffell (2008), Feucht and Opelz (1996), Hourmant et al. (2005) have confirmed that HLA antibodies, especially DSA, are the major cause of acute AMR and chronic rejection, the latter accounting for most graft failure. Even though the risk of graft failure is positively correlated with DSA level, the association can vary between patients. In the acute setting, transplantation across high DSA levels may result in 50% graft loss, but data based on

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the currently available assays cannot discriminate between successes and failures (see reference Puttarajappa et al. (2012)). Likewise, in the chronic setting there is not a clear relationship between the occurrence of AMR and the DSA as detected in the blood.

Preformed DSA, compared with de novo DSA, usually show dramatic rises and falls over a period of a few days after operation. However the dynamic behaviour of post transplant DSA varies from case to case; even different DSA in the same patient (targeting different HLA) can reveal diverse patterns. We have obtained a unique dataset with detailed antibody levels spanning three to six months starting around 10 days before transplantation. A previous study in Higgins et al. (2009) carried out for this data has suggested that repetitive patterns occur in patients with or without acute AMR episodes: some DSA time series show a rapid rise during the first week followed by a rapid fall to almost undetectable levels, which then remain low. This finding was striking; in many of these patients, the DSA had been persistent for many years before transplantation, and therapies used experimentally have been unable to stop antibody production before transplantation. Therefore an understanding of this remarkable phenomenon could lead to 'desensitisation' of a patient before transplantation, potentially even removing the antibody barrier to engraftment completely. However this phenomenon has only recently been described, and it is not at all clear what the immunological mechanisms might be. There are several hypotheses that might explain the disappearance of DSA, each of which is potentially difficult and time consuming to test. The focus of our work is on the development of a dynamic model to describe the dynamics of DSA after transplantation, hypothesising that these results would enable intelligent application of laboratory testing to patient samples, ultimately leading to therapies which might be able selectively to control this antibody response and improve clinical transplant outcomes.

2. DATA DESCRIPTION

Twenty-one post transplant DSA time series from twelve patients who underwent antibody incompatible renal transplantation between 2003 and 2007 were investigated in this study. The group characteristics and details of therapy have previously been described in Higgins et al. (2009). Note that some of our patients had multiple DSA. Twelve DSA time series belong to six patients that experienced acute AMR in the first 30 days after transplantation (AMR group), and nine DSA time series belong to the other six patients who did not have an acute AMR (no-AMR group). We selected these DSA time series based on the common feature of a rapid rise and fall in DSA levels after kidney transplantation. Rejection episodes were diagnosed by renal biopsy or clinically if there was rapid onset of oliguria with a rise in both serum creatinine and in DSA levels. Serum samples for DSA analysis were taken daily in the first three to four weeks, as most dynamic behaviour appears during that period, and sampling becomes more sparse later when antibodies tend to be more stable. Peak DSA was defined as the highest level of DSA within the first six weeks post transplant. The antibody level was measured using microbead assay manufactured by One Lambda Inc (Canoga Park, CA, USA), analysed on the Luminex platform (XMap 200, Austin, TX, USA). The assay measures the Mean Fluorescence Intensity (MFI) which corresponds to antibody level although their relationship is linear only over a limited range. As described in Higgins et al. (2009), when the MFI value is higher than 10,000 AU (arbitrary units) and below about 1,000 AU, the linear correlation breaks. An example of the MFI time series for a patient from a no-AMR group is shown in Fig. 1, where day 0 is the day of transplantation.

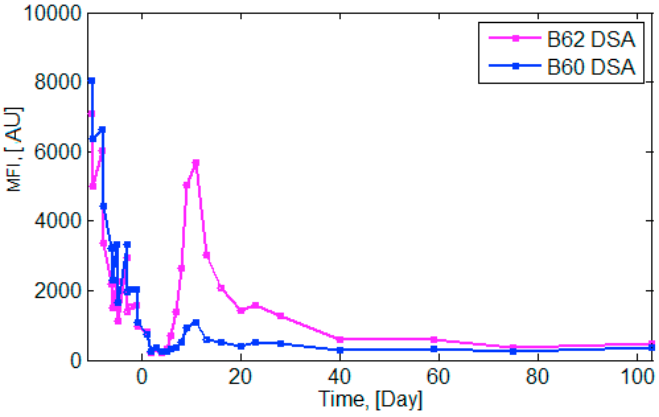

Fig. 1. Mean fluorescence intensity measurement time series of DSA 62, DSA 60 from a patient from no-AMR group. Each measurement is indicated by a cross.

The initial drop in DSA levels before day 0 was caused by double filtration plasmapheresis that started 10 days before transplantation. On average, two to five alternate day sessions were performed before operation to remove the existing DSA. The rise in DSA over the first few days after transplantation was partly caused by plasmapheresis stopping, but also by an increased rate of synthesis of DSA, the expected immunological memory response. The different patterns of falls can be easily distinguished from B62(DSA) and B60(DSA) in Fig. 1. A previous study done by Higgins et al. (2009) suggested that the fall is greater in the AMR group compared with the no-AMR group, and the rate of fall of DSA exceeds the rate of fall of other non-DSA antibodies. In this work we concentrate our attention on the falling dynamics from the peak, which is typically reached within two weeks after operation, down to a steady state.

3. MODELS AND METHODS

3.1 Model formulation

DSA falls in the antibody response to a transplanted kidney during the acute stage after operation for people with and without AMR can be described by the following model:

$$\frac{\mathrm{d}^n}{\mathrm{d}t^n}x_t + \theta_n \frac{\mathrm{d}^{n-1}}{\mathrm{d}t^{n-1}}x_t + ...\theta_2 \frac{\mathrm{d}}{\mathrm{d}t}x_t + \theta_1 x_t - \theta_0 = 0 \quad (1)$$

$$y_t = x_t + \varepsilon_t \quad (2)$$

Eqn. (1) is an evolution equation of nth order, where x_t is a function of t that describes the MFI dynamics,

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