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A new data-driven model for post-transplant antibody dynamics in high risk kidney transplantation

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ABSTRACT

The dynamics of donor specific human leukocyte antigen antibodies during early stage after kidney transplantation are of great clinical interest as these antibodies are considered to be associated with short and long term clinical outcomes. The limited number of antibody time series and their diverse patterns have made the task of modelling difficult. Focusing on one typical post-transplant dynamic pattern with rapid falls and stable settling levels, a novel data-driven model has been developed for the first time. A variational Bayesian inference method has been applied to select the best model and learn its parameters for 39 time series from two groups of graft recipients, i.e. patients with and without acute antibody-mediated rejection (AMR) episodes. Linear and nonlinear dynamic models of different order were attempted to fit the time series, and the third order linear model provided the best description of the common features in both groups. Both deterministic and stochastic parameters are found to be significantly different in the AMR and no-AMR groups showing that the time series in the AMR group have significantly higher frequency of oscillations and faster dissipation rates. This research may potentially lead to better understanding of the immunological mechanisms involved in kidney transplantation.

1. Introduction

Kidney transplantation is proven to be the best treatment for renal failure and success is dependent on the reaction of the immune system primarily against human leukocyte antigen (HLA) proteins of the transplant. The HLA system is extremely complex; it is unusual to find two unrelated individuals with the same HLA type and only a minority of the transplants in the UK are *fully matched* for HLA tissue proteins [1]. Conventional transplantation is facilitated by immunosuppression which targets cellular components of the immune system.

A significant number of patients develop antibodies to HLA following exposure to non-self HLA from pregnancy, blood transfusion or previous kidney graft [2,3]. These antibodies exist as multiple isoforms but it is Immunoglobulin G (IgG) which is deemed to be most detrimental to transplant outcome [4]. Such IgG, termed donor-specific antibody (DSA), when directed at a current or prospective donor HLA, can persist for years and are a barrier to transplantation because they can cause immediate, early, and late rejection. Safe transplantation of potential recipients with high levels of circulating DSAs is an ongoing problem resulting in prolonged waiting times for transplantation [5]. Ideally, such recipients should receive a transplant from an antibody compatible donor but because of a donor shortage this is seldom possible.

Innovative clinical protocols and techniques have been developed [5–7] to allow transplantation of such highly sensitised patients by removal of DSAs immediately before the transplant [2,8]. Complete elimination of preformed HLA DSAs is not possible and, because of immunological memory, post-transplant DSA resynthesis can still result in severe acute antibody-mediated rejection (AMR) and an increased risk of graft loss. The mechanisms underlying the control of antibody production are poorly understood and treatments given to patients with AMR can be ineffective. In recent years, a number of publications [9–11] have confirmed that HLA antibodies are the major cause of acute AMR and chronic graft

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failure. Even though the risk of acute rejection and chronic graft failure is positively correlated with high DSA levels, the association can vary between patients. In the acute setting, transplantation across very high DSA levels may result in 50% graft loss, but data based on the currently used antibody detection assays cannot reliably predict the outcome [12]. Likewise, in the chronic setting there is not always a clear relationship between the occurrence of AMR and the detection of circulating DSAs [13,14].

Our group has investigated early DSA dynamics in these high risk transplants because the nature of their response is likely to profoundly affect clinical outcomes [2,8,15]. We have observed that the dynamic behaviour of post-transplant DSAs varies from case to case, and even different DSAs in the same patient (targeting different HLA) show diverse patterns. Development of a strong mathematical approach to describe the dynamics of the preformed DSAs has not yet been attempted. This is because white box models, i.e. physiological models, are not yet feasible due to the complexity of underlying immunological responses to transplants. Data-driven models, on the other hand, require both an accurate method of measuring the DSAs in human sera and an appropriate mathematical framework for the development of the model from limited and complex sets of data.

The possible mechanisms underlying changes in the levels of DSAs are complex and the DSAs levels cannot easily be measured in the laboratory. DSA levels may change because of rises and falls in the rate of production. This itself could be related to changes in the populations of antibody-producing cells (plasma cells and memory B lymphocytes), and these cells could be formed pre-transplant and/or recruited from less mature lymphocyte populations post-transplant [16]. Falls in the levels of DSA post-transplant are very interesting, as these may occur much faster than the 'natural' rate of antibody clearance from the body (thought to have a half life of about 20–30 days [17]). Mechanisms associated with reductions in antibody levels could include absorption of antibodies onto HLA molecules on the graft [18] – it is known that the levels of HLA on a graft may increase post-transplant, but this cannot yet be quantified. Some HLA is shed by the graft, so antibodies could be absorbed in the circulation. It is known that one physiological method used by the body to control antibody levels is to produce antibodies that block other antibodies (idiotypic antibodies), and production of idiotypic antibodies could explain the falls in DSA post-transplant [19]. However, as with other potential regulatory mechanisms, it is currently hard to measure idiotypic antibodies accurately. Thus, mathematical modelling of changes in DSA levels may indicate where the efforts involved in developing new laboratory assays might be best directed, and once appropriate assays are available, the modelling may help in the interpretation of results of the assays at different time points. This could be particularly important in relation to falls in DSA levels, since this is a key clinical objective that is currently not achievable in clinical practice.

It has recently been recognised by the transplant community [2,20] that post-transplant screening for anti-HLA antibodies could be an important tool for monitoring of transplant recipients. Highly sensitive and specific assays using purified HLA protein have been developed in recent years. This development in assays meets the increasing need for monitoring post-transplant DSAs [21] and opens up opportunities to develop data-driven mathematical models for the evolution of antibodies after transplantation.

A unique dataset with detailed antibody measurements spanning three to six months, starting around ten days before transplantation has been obtained by our group. A previous analysis [2] of these data revealed various patterns of antibody dynamics, both with or without acute AMR. Some DSA time series show a rapid rise during the first two weeks followed by a rapid fall to almost undetectable levels, which then remain low. This finding is striking: in many of these patients, the DSAs had persisted for many years before transplantation, and therapies used experimentally have been unable to stop antibody production before transplantation. A better understanding of this phenomenon could therefore have practical benefits.

The aim of this work is therefore to describe the pathological early antibody response in mathematical terms and we hypothesize that this approach might enable a more intelligent application of laboratory testing and suggest therapeutic approaches to selectively control this antibody response and improve clinical transplant outcomes. To take full advantage of the data available, we have developed a data-driven model based on differential equations that reflects the continuous nature of the underlying immunological process [22]. The usefulness of the model for classification between patients with and without AMR was also investigated.

Data from the patients in this series were analysed in relation to a single outcome measure, namely the occurrence of early acute AMR. This is a key early outcome in antibody incompatible transplantation (AIT), as it is associated with the levels of immunosuppression required in the early post-transplant period, and is also associated with short and long term graft survival.

The structure of the paper is as follows. Section 2 gives details on the data and presents visual analysis of the variety of dynamic antibody responses to transplantation. Section 3 explains the methodology for model formulation and parameter estimation. Section 4 presents the final model and detailed analysis of systems parameters. Section 5 summarises the results, justifies the need for further work and outlines the relevance of the model for kidney transplant management.

2. Data description and visual analysis of dynamic patterns

Data from twenty-three patients who underwent renal AIT at University Hospitals Coventry and Warwickshire (UK) between 2003 and 2012 were analysed in this study. The data were comprised of time series of DSA evolution over a period of about ten days before and six months after transplantation. Serum samples for DSA analysis were taken almost daily in the first three to four weeks, as most dynamic behaviour occurs during that period, and sampling became more sparse later when the antibodies tended to be more stable. Antibody levels were measured using the 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 [2], when the MFI value is higher than 10,000 AU (Arbitrary Units) and below about 1000 AU, the linear correlation breaks.

Some of the patients had multiple DSAs targeting different HLA, so the total number of post-transplant time series available for this analysis was *thirty-nine. Twenty-seven DSA time series* belong to fourteen patients that experienced episodes of acute AMR in the first thirty days after transplantation (AMR group), and *twelve DSA time series* belong to the other nine patients who did not have an episode of AMR (no-AMR group). Rejection episodes were diagnosed by renal biopsy or clinically if there was rapid onset of oliguria with a rise in both serum creatinine and DSA levels [2]. In patients receiving HLA antibody-incompatible grafts, the incidence of AMR was 30–40% [15]. Although AMR can be severe and can eventually result in graft failure, it usually develops slowly over a period of several days. This gives an opportunity to detect AMR at an early stage and treat it, resulting in better outcomes [8]. The group characteristics and details of therapy have previously been described [2]. A smaller dataset including *twenty-one* time series from the first twelve patients in the cohort was considered in our preliminary study [23].

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