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THE SINGNIFICANCE OF IGG SUBCLASSES IN HLA ANTIBODY INCOMPATIBLE KIDNEY TRANSPLANTATION.

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Introduction. Antibodies in prospective kidney recipients can be a barrier to transplantation. Annually this stops about 250 living donor transplants in the UK. To address this we have pioneered the development of HLA (human leucocyte antigens – transplantation antigens) antibody incompatible transplantation (AiT) in the UK. Our observations in over 70 such procedures are that although pretransplant antibody reduction is required to avoid complement mediated hyperacute rejection or severe early graft damage, an early post-transplant antibody response occurs in most cases and in about half of these rejection is diagnosed. Our aims were to investigate whether the subclass of both pre and post-transplant donor-specific antibodies (DSA) and/or IgG subclass switching associates with subsequent early rejection. The ultimate purpose being to provide evidence for improved clinical management. Methods 52 previous AiT cases were selected as two equal groups of rejectors and non-rejectors. Rejection was diagnosed on the basis of clinical symptoms and/or histology. Serum samples were collected daily post-transplant and total level of HLA-specific antibodies (as bead fluorescence – MFI) determined by single antigen bead assay. From this the post-transplant antibody peak samples was identified for each case. IgG1, 2, 3 and 4 HLA specific antibody levels were determined for all pretreatment, pretransplant and post-transplant peak samples. Results We have previously reported that in these cases the higher pretreatment total IgG levels predict rejection and while IgG1 was the most common subclass, followed in order by IgG2, IgG3 and IgG4, IgG4 was restricted to the group of recipients who subsequently went on to have rejection episodes (6/26 vs 0/26, p=0.001). Examination of the difference in incidence of a response for each subclass (higher level at peak vs pre-treatment) showed that the IgG1 response provides the strongest correlation with rejection (HLA Class I DSA p=0.026, HLA Class II p<0.001) with an IgG2 response only significant for Class II DSA associated rejection (p=0.041). Finally we observed 8 rejector cases class switching to IgG2 compared with 2 non-rejectors (p=0.03). Conclusion This work demonstrates that IgG DSA subclass distribution is a predictor of early rejection and provides valuable insights into the immunology of rejection in this setting. The association of Ig4 with rejection is strongly suggestive of the more chronically sensitised cases being the most likely to reject with implications in patient selection and treatment. IgG1 is the predominant subclass both pre and post-transplant. The appearance of IgG2 (relatively poor at complement fixation) with early rejection implies that complement mediated damage may not necessarily be central to this rejection process. This is supported by the association of IgG4, the weakest complement fixing IgG with rejection and lack of association with IgG3, the strongest complement fixing subclass. Alternatively the presence of specific IgG subclasses may reflect specific T cell dependent processes. Indeed we have shown that in these cases, rejection is often most effectively treated with anti-T cell agents such as OKT3

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CLINICAL SIGNIFICANCE OF DE NOVO PRODUCTION OF HLA DONOR-SPECIFIC ANTIBODIES IN KIDNEY TRANSPLANTATION.

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Introduction. Several studies have shown that de novo production of HLA donor-specific antibodies (DSA) is predictive of adverse short- and long-term outcome in kidney transplantation. At the same time, there is increasing evidence that HLA-DSA do not inevitably cause graft injury even if antibody production persisted for many years. Aim of this study was to evaluate whether HLA-DSA with different characteristics may have different clinical impact on kidney allograft outcome. Methods. In 498 kidney transplanted patients, who received a cadaver-donor kidney transplant at the Transplant Center of "Tor Vergata" University of Rome between January 1990 and December 2008 we analyzed de novo production of HLA-DSA by cytometric solid-phase techniques (FlowPRA class I and II Screening Beads and Luminex-Single Antigen Beads). DSA strength was assessed using Quantiplex Beads and Standard Fluorescence Intensity (SFI) values. Follow-up for both HLA-DSA and graft clinical course ranged from 1 to 17 years. Results. Seventy-seven (15.5%) of the 498 patients developed HLA-DSA. Anti-Class I DSA were only found in 21 patients, anti-Class II DSA in 46 patients and both anti-Class I & II in the remaining 10 patients. In 79% (44/56) of the anti-HLA class II positive patients, anti-DQB1 and/or -DQA1 DSA were found. In 29 of these patients, anti-DQA1/DQB1 DSA were exclusively present. Correlating graft outcome and DSA status, we evidenced a strong negative impact of de novo DSA production on graft function; graft failure (GF) was significantly higher in DSA-positive patients than in the DSA-negative ones (39% vs. 13%; P < 0.0001). However, only 30 of the 78 patients with de novo HLA-DSA production lost their graft. Sixteen (20%) patients suffered chronic allograft dysfunction (CAD) and the remaining 31 (40%) showed functioning graft (FG) during all the follow-up period from DSA appearance. As for patients who only produced anti-DQA1/DQB1 DSA, 82% of anti-DQB1 positive patients suffered GF or CAD while all anti-DQA1 positive patients had FG (P = 0.001). Considering epitope specificity of DSA, we evidenced that GF-group patients had a higher incidence of wide antibody patterns specific for "public epitopes" of the HLA mismatched molecules of the graft than FG-group patients (80% vs. 45%, P = 0.0079). Finally, considering the strength of DSA, high SFI values (> 100.000) were found in 88% of GF-group patients vs. 45% of FG-group ones (P = 0.001). Conclusions: de novo production of HLA-DSA is associated with poor graft survival but also occurs in patients with good graft course. Characterization of DSA strength/specificity and identification of sensitizing HLA-epitope is helpful in identifying patients who need implementation of therapeutic measures to prolong graft survival.

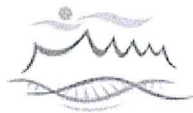**Disclosure:** All authors have declared no conflicts of interest.

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