



# Anti-donor immunoglobulin G subclass in liver transplantation

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**Abstract:** Immunoglobulin G (IgG) subclasses in human health and immunity have only been sporadically studied in the half century since their discovery. Different patterns of IgG subclass production are seen if the immune response is deviated towards type 1 versus type 2. The current state of our knowledge of IgG subclasses in liver transplantation is reviewed here. While several studies have been conducted in liver disease, only four relatively small studies have been undertaken in liver transplant recipients. Total IgG4 elevation in serum is related to sclerosing pancreatico-cholangiopathy that is sensitive to treatment with steroids. Conventional immunosuppressive regimes, especially with a combination of tacrolimus and sirolimus, reduce the production of all IgG subclasses after transplantation but it is not known if they deviate the immune response. Presence of anti-donor IgG3 before transplantation, or its expansion after transplantation, has been associated with rejection and liver graft loss. Anti-GSTT1 IgG4 production after transplantation is associated with *de-novo* immune hepatitis. Greater knowledge of anti-donor IgG subclass responses after transplantation will allow us tailor novel treatments for greater effect.

**Keywords:** Anti-donor; immunoglobulin G subclass; liver transplantation

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This review arises out of an unexpected outcome of a contentious organ allocation for transplantation. A patient with polycystic liver and kidney disease requiring an urgent transplantation because of combined organ failure was offered grafts from a donor, against whom the antihuman globulin augmented, complement-dependent cytotoxicity, cross-match was strongly positive. Because of previously reported successful transplantation of crossmatch-positive liver-kidney transplantation and the patient's deterioration, the offer was accepted. This decision was disputed by some members of the kidney transplant team. The other kidney, from the same donor, was accepted for a cross-match negative patient who had rejected a previous kidney graft 11 years after transplantation. Objections were noted and the transplantations proceeded under close observation. The liver-kidney grafts survived without rejection. The kidney-only graft was lost to hyperacute rejection. *De-novo* production of non-complement fixing anti-donor immunoglobulin (Ig) M was transiently noted in the liver-kidney recipient (1). On the other hand, preformed anti-donor IgG subclass 3 was found retrospectively to

have been present in the kidney-only recipient before retransplantation and to have increased after it. Can we explain the difference in outcome through a better understanding of donor specific antibodies (DSA)? The effect of DSA is well characterized in kidney transplantation but their effect on transplantation of the liver is less certain. We thought this difference might be explained by the prevalence of DSA which is much higher in candidates for kidney transplantation than liver transplantation. However, we were unable to detect an effect of DSA on survival of liver retransplantations where the prevalence of DSA was high (2). Therefore we will turn our attention in this review to the type of the immune response to transplantation, in particular to class-switch.

Discoveries 50 years ago are still being applied today. At the same time that Terasaki was investigating the role of antibodies, measured by lymphocytotoxic cross-matching, in transplantation (3), the husband and wife team, Kimishige and Terako Ishizaka, discovered the IgE isotype and described its role in allergy (4). Gradually mechanisms were elucidated for naive B cells, which normally produce IgM,

to recombine their DNA during activation to produce a particular Ig isotype (IgG, IgA or IgE), according to the class of immune response. The process was called 'class-switch' and its role in transplantation was not appreciated for over 20 years. The effector functions of IgE in atopy were clearly different to those of IgG, which was thought to predominate in transplantation. In 1987, two types of T helper cell (TH) activation were described: TH1 which was induced by virus and believed to cause rejection and TH2 which was induced by parasites and may allow persistence (5). The pattern of cytokine production distinguished TH1 from TH2 and the cytokines seemed to explain their function. The interaction of B-cells and T-cells was known so that the alignment of TH deviation with Ig class-switch was quickly realized. The teleology of having two paths of adaptive immune response needs to be considered. The best guess is that while the type 1 response is the default protective response against foreign invaders such as viruses, the type 2 response is required to allow a pregnancy, which is a haplo-identical transplant after-all, to proceed to completion. Evidence for this continues to be found (6). Parasites were thought to exploit the availability of the type 2 pathway to avoid rejection. *Nippostrongylus brasiliensis* is known to induce class-switch production of IgE and we were able to show that inoculation of rat kidney transplant recipients with the parasite resulted in class switch (IgE) and TH2 cytokine production. Type 2 deviation of the immune response after transplantation was associated with prolongation of graft survival (7). Farges and colleagues were the first to investigate class-switch in clinical liver transplantation. In a small group of liver transplantations, they found higher levels of preformed IgE in patients who avoided rejection but no difference in IgM, IgG or IgA (8).

Animal models of transplantation have pitfalls if results are directly transferred to the human. Spontaneous acceptance of liver transplants, which has been demonstrated in the mouse, makes us cautious of applying therapies tested only in murine models. On the other hand, seemingly bewildering observations can open unexpected lines of research. Kidney transplantation from C57BL/6 mice to untreated BALB/c mice results in loss of the graft to rejection within approximately 8 days whereas BALB/c kidneys survive more than 100 days in untreated C57BL/6 mice (9). BALB/c and C57BL/6 are immunocompetent and both make DSA. However the DSA IgG subclass pattern produced by each strain is different so that we are able to say that murine anti-donor IgG2a is associated with

rejection whereas murine IgG1 is associated with transplant tolerance. Humans and mice have 4 subclasses of IgG but with differing nomenclature. While the light chain of IgG is conserved, differences in the heavy chain determine the subclasses. DNA recombination is similar to that seen with IgM to IgE class-switch so that sequence of production is IgM followed by IgG3, then IgG1, then IgG2, and finally IgG4 with corresponding diminution in complement fixation. For example, an amino acid switch (proline to serine) at the core hinge reduces the complement fixing ability of human IgG1 to that of IgG4. Human IgG3, followed by IgG1, is the most potent complement binder of the subclasses (10). Human IgG4, the subclass present in the least concentration, is predominately expressed in association with chronic antigen stimulation, where it inhibits complement (C1q) binding.

All of the clinical studies to date of DSA IgG subclasses in liver transplantation are either underpowered or retrospective. Farges and colleagues described DSA IgG1 and IgG2 subclass development in 6 of 9 liver recipients but could not determine an association with rejection (8). The index case described above involved a pair of kidneys. One kidney was hyperacutely rejected by a recipient who had DSA IgG3 before transplant; the mate kidney survived despite a positive CDC cross match because it was transplanted simultaneously with a liver graft from the same donor (1). The liver-kidney recipient did not show IgG3 predominant DSA but had DSA in all subclasses, mostly IgG2. We wondered if the difference in outcome was related to the different pattern of DSA IgG subclass in the recipient. Therefore we then compared 6 liver recipients with 6 kidney recipients and 6 combined transplants, measuring changes in DSA Ig subclasses on post-transplant day 10 and 100 compared to the level measured before transplantation. None of the liver recipients experienced rejection. We did not see any pattern associated with the type of organ transplanted, if no rejection occurred. Three kidney recipients experienced rejection which appeared to be associated with an increase in DSA IgG3 production. One of these kidneys was lost to rejection and in the two survivors, an IgG4 level increase was seen on day 100 (11). The role of DSA IgG3 in rejection and graft loss after liver transplantation was confirmed by O'Leary and colleagues in a large retrospective study (12). The mechanism was determined to be DSA IgG3-induced C1q-fixation (13). An interesting feature of our study was the fact that all of the liver recipients received immunosuppression with a combination of tacrolimus and sirolimus (11). This

combination has been shown to suppress total DSA formation after transplantation, so long as drug levels remain stable (14). The effect of immunosuppression upon deviation of the immune response and the pattern of IgG subclass expansion after liver transplantation, or indeed after transplantation of any solid organ, has not been studied yet.

The presence of IgG subclasses in humans has been known for a long time (15). Their role in a variety of auto-immune diseases, including those affecting the liver, has been studied. In 1999, Erkelens and colleagues described sclerosing pancreaticholangitis in 4 patients that responded well to steroid therapy (16). Hamano and colleagues discovered high IgG4 levels in these patients (17). The finding has been important clinically as a subset of patients previously diagnosed as having primary sclerosing cholangitis or pancreatic cancer have been spared unnecessary surgery and chemotherapy with effective steroid treatment. We noted a small expansion of IgG4 production after organ transplantation but it has not been related to post-transplant cholangiopathy yet.

Other liver diseases were found to be related to IgG subclasses. Alcoholic liver disease is associated with high serum concentrations of IgA and IgE and low IgG. An experimental study confirmed the expansion of IgE and reduction of IgG with administration of alcohol to mice (18). Production of IL-13 but not of interferon-gamma suggested a type 2 deviation of the immune response. Reductions were seen in all IgG subclasses in a murine strain dependent manner (18). No parallel study in humans has been done yet.

Yang and colleagues have conducted several studies of the human immune response to hepatitis B virus (HBV). They found higher level of IgG1, IgG3 and IgG4 in 104 HBV carriers compared to 439 individuals who cleared the virus (19). Among the carriers, IgG1 was higher if there was evidence of inflammation.

The glutathione S-transferase (GST) supergene family influences metabolism of drugs and other toxins by the liver and variations have been associated with cancer. Wang and colleagues performed a meta-analysis which showed null genotypes of GST polymorphisms, M1 and T1, to be associated with an increased risk of hepatocellular carcinoma in Asians, especially where both polymorphisms are absent (20). Transplantation of a GSTT1 positive liver into a GSTT1 null recipient results in the production of anti-GSTT1 antibodies (21). Aguilera and colleagues have studied this phenomenon. They believe that 25% of anti-GSTT1 antibody producers after transplantation develop *de-novo* immune hepatitis. They studied 12 recipients with

post-transplantation immune hepatitis compared to 6 recipients with anti-GSTT1 antibodies who did not have the disease. IgG4 positive plasma cells were considerably increased in biopsies showing immune hepatitis and higher levels of circulating anti-GSTT1 IgG4 were found (22).

In summary, IgG subclasses have only been sporadically studied in liver disease and transplantation but tantalizing signals are emerging. Total IgG4 elevation in serum is related to pancreaticholangiopathy that is sensitive to treatment with steroids. Conventional immunosuppressive regimes, especially with a combination of tacrolimus and sirolimus, reduce the production of all IgG subclasses after transplantation but it is not known if they deviate the humoral response. Presence of DSA IgG3 before transplantation, or its expansion afterwards, has been associated with rejection and liver graft loss. Anti-GSTT1 IgG4 production after liver transplantation is associated with *de-novo* immune hepatitis. Future studies of IgG subclass responses in liver disease and transplantation will suggest novel treatment pathways.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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