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What's new in clinical solid organ transplantation by 2013

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Abstract

Innovative and exciting advances in the clinical science in solid organ transplantation continuously realize as the results of studies, clinical trials, international conferences, consensus conferences, new technologies and discoveries. This review will address to the full spectrum of news in transplantation, that verified by 2013. The key areas covered are the transplantation activity, with particular regards to the donors, the news for solid organs such as kidney, pancreas, liver, heart and lung, the news in immunosuppressive therapies, the news in the field of tolerance and some of the main complications following transplantation as infections and cancers. The period of time covered by the study starts from the international meetings held in 2012, whose results were published in 2013, up to the 2013 meetings, conferences and consensus published in the first months of 2014. In particular for every organ, the trends in numbers and survival have been reviewed as well as the most relevant problems such as organ preservation, ischemia reperfusion injuries, and rejections with particular regards to the antibody mediated rejection that involves all solid organs. The new drugs and strategies applied in organ transplantation have been divided into new way of

using old drugs or strategies and drugs new not yet on the market, but on phase I to III of clinical studies and trials.

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Key words: News in transplantation, kidney transplantation, pancreas transplantation, liver transplantation; Heart transplantation; Lung transplantation; New immunosuppressant; Tolerance

Core tip: Basic and clinical science in solid organ transplantation are continuously evolving. In this review we outlined the most important innovative findings recently discovered. The period of time chosen was 2013, but attention has been paid to the outstanding conferences held in 2012, but published in 2013, as well as to the conferences and meetings held in 2013 but published in 2014. We are aware that when this study will be published, new interesting and relevant findings will have been discovered. The science is flowing continuously, nevertheless analyzing in depth a short period of time can give useful information to the readers.

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INTRODUCTION

Innovative and exciting advances in the clinical science in organ transplantation continuously realize as the results of studies, clinical trials, international conferences, consensus conferences, new technologies and discoveries. This review will address to the full spectrum of the news in transplantation, that verified by 2013 and the key areas covered for every organ as the organ transplant activity,

the organ survival rates, the organ preservation and allocation, the new immunosuppressive regimens, the new immunological findings and the most important complications following organ transplantation.

The organ procurement transplant network/scientific report transplant recipients (OPTN/SRTR), the most wide and extensive registry on transplantation, by the end of 2013 published the complete data^[1] concerning organ transplantation for 2012 and allowed for several considerations on the transplant activity. In particular, in the 2013 report, for the first time, OPTN/SRTR has undertaken to publish the worldwide transplant rates as part of its annual data report^[2].

This report found that the transplant counts and rates vary among the countries around the world for different reasons: (1) Differences in the rates of end-organ disease. Country to country variability in the underlying incidence of end-organ disease can be expected to affect the organ transplant rate. However other factors undoubtedly play a role in determining the transplant rates. For example the incidence of end stage renal disease (ESRD) in Norway in 2009 was one third of the incidence in the United States. Nevertheless, in 2010, the rates of kidney transplant were similar in Norway and the United States, probably due to the very high activity related to living donor that characterizes the Norway; (2) Socioeconomic factors. There is a strong correlation between the Human Development Index (HDI) and the rate of deceased and living donor kidney transplants among the world health organization member states^[3]. Similarly, the rates of liver transplant are lower in the countries with lower HDIs; (3) Cultural differences. An example is Japan that has a very high HDI, but lower rate of kidney transplants; and (4) Thoroughness of the transplant reporting, that varies by country.

Worldwide, use of living kidney donors varies widely, from less than 10% to more than 75%. The rates of liver transplant have increased by more than 10% in several countries and declined in very few countries. In the past 5 years, the lung transplant rates have remained stable. The heart transplant rates changed little in the majority of countries.

NEW INSIGHTS FOR DONORS

In 2012 the number of deaths eligible for organ recovery for transplantation was lower than 2011 and 2010^[4]. Similarly the mean number of organs transplanted per donor in United States in 2012 was 3.02, lower than in 2011 and 2010. Numbers of hearts and lungs procured for transplant but not used are smaller than the numbers of kidneys, pancreas and livers because the former organs are recovered only after the acceptance by the transplant center.

Data from OPTN/SRTR show that the number of Standard Criteria Donors (SCD) have remained about the same in United States and Europe, but there has been a dramatic increase in older donors and organs classified as donation after cardiac death. Overall, among deceased donors there is an organ donor shift^[5]. Indeed, the

percentage of all donors who are SCD is on the decline and there is an increase in Expanded Criteria Donors (ECD).

This shift could impact on the outcomes and more research is necessary to improve the quality of organ used for transplant and to optimize the use of a further expanded donor pool.

A wide, retrospective study from Heaphy *et al*^[6] confirms this issue, as the donor quality has significant interactions by race, primary diagnosis and age. Another study^[7] suggests that the judicious use of ECD kidneys may be an appropriate strategy to expand the donor pool minimizing the effects upon the outcomes.

Improving the organ cold storage by machine perfusion (MP) has been proposed to improve the solid organ outcomes. Especially in liver^[8], heart and lung transplantation^[9], the MP seems to be a promising tool to improve post-operative outcome, but a general evidence-based recommendation for or against on application of MP, cannot be given due to the lack of highest level of clinical evidence.

In addition to the above mentioned shift among deceased donors, recently, at least in United States, a decline in living kidney donation rate has been observed. This decline is about 13% per year and is more pronounced among blacks, men, younger adults, siblings and parents^[10]. This fact warrants an action by transplant centers and national governments, also because another wide study^[11] documented that the public is supportive of the living donation and in favor of protecting the health and safety of living donors.

A barrier to solid organ transplantation is often represented by the pre-transplant presence of donor specific antigens (DSAs) in the recipient sera. This fact is well known for the kidneys but has clinical relevance also for liver, heart and lung transplantation^[12].

In such condition, for deceased donor kidney donation, the technique of acceptable human leukocyte antigen (HLA) mismatches has shown its efficacy. Two 2013 large studies proved its transnational efficacy^[13,14].

In the case of the living kidney donation the presence of preformed antibodies may represent a relevant barrier to transplantation. In kidney transplantation, this barrier may be overcome by the network called kidney paired donation (KPD). Originally conceived as simple two-way reciprocal exchange between AB0 incompatible, KPD has evolved to include complex, multicenter, discontinuous chains, with transcontinental transport of kidneys. To date the majority of the researches performed on KPD has involved computer generated mathematical optimization algorithms. Several 2013 papers confirm the effectiveness of such network^[15-17].

NEW INSIGHTS FOR KIDNEY

Main kidney related issues considered in 2013 publications have been: the kidney and recipient graft survivals, the impact and consequences of ischemia-reperfusion injury, the antibody mediated rejection (ABMR) and the new

techniques involved in rejection diagnosis.

Transplant activity and kidney graft survival

According to OPTN/SRTR data, the shortage of kidneys for transplant remains a major problem for patients with ESRD. The number of candidates on the waiting list continues to increase, while the organ donation numbers remain flat^[18]. Many kidneys recovered for transplant are then discarded for organ related problems and the discard rate is increasing. Living donation rates have been unchanged for the past decade. For both living and deceased donor recipients, the early post-transplant results have shown ongoing improvement.

For the first time, the graft survival rates have been systematically compared between Europe and United States. Utilizing data from OPTN/SRTR for United States and data from the Collaborative Transplant Study for Europe, the 1, 5 and 10-year graft survival rates have been compared among Europeans and White, African and Hispanic Americans^[19]. While the 1-year graft survival rate was similar, the 5 and 10-year graft survival rates were considerably higher for Europe than for any of the three United States populations. Differences increased beyond three to four years after transplantation and these differences are not explained by differences in baseline patient characteristics. Studies are needed to identify factors contributing to the observed graft survival differences. Previous studies have documented that the limitations in access to immunosuppressive medications^[20,21] and related compliance^[22] are important determinants of long-term graft failure. Indeed, in the past the extension of immunosuppressive coverage in the US has shown to effectively reduce the income-related disparities in graft survival^[23]. An United States study in 2013 examined the impact of Community risk factors on the kidney transplant outcomes^[24]. The study documented that community risks are powerful factors associated with processes of care; and represent important considerations for developing effective interventions.

Ischemia-reperfusion injury

The Food and Drug Administration (FDA) held an open public workshop in September 2011 to discuss the current state of science related to the effects of ischemic reperfusion injury (IRI) on the outcomes in kidney transplantations. The summary of the workshop has been published in 2013^[25]. The conclusions were that IRI impacts on graft survival and a better understanding of the underlying mechanisms is needed. Medical products to impact on IRI are urgently needed, but their development relies on both clinical and non-clinical researches. Also qualification of biomarkers is essential to elucidate the mechanisms^[26].

Necroptosis in immunity and IRI have been principally studied in 2013^[27-30]. Pathways of regulated necrosis (RN), an alternative to apoptosis have been recently described. The best studied RN pathway, the necroptosis, is triggered by perturbation of caspase-8-mediated apoptosis. In this condition the necroptosome is assembled and quickly leads to the necrotic-type cell death, release of the cell

death-associated molecular patterns and severe organ damage. Interference with necroptosis (*e.g.*, by necrostatin) is more likely to be of clinical benefit in situations in which the reperfusion damage can be anticipated as solid organ transplantation.

Antibody-mediated rejection

Recent studies indicate that ABMR is among the most important barriers to improving long term outcomes principally in kidney transplantation, but in other solid organs as well^[31].

Additionally new knowledge in ABMR pathophysiology, classification, diagnostic techniques and therapeutic approaches has merged. While the new therapeutic approaches will be described in the therapy chapter, the other issues will be treated in this paragraph.

A relevant and new finding is that not only the donor specific antibodies anti HLA (DSAs-HLA) are involved in ABMR. The antibodies against other molecules^[32,33] and also polyreactive antibodies directed against apoptotic cells may cause ABMR^[34].

The antibodies cause graft damage by endothelial cell injury mediated by the activation of complement. C4d is a split product of C4 activation and is often present on endothelial cells in ABMR. Sis *et al.*^[35] described that 60% of kidneys with high endothelial activation and injury transcripts (ENDATs) and chronic ABMR were C4d negative. A recent microarray study from Sellarés *et al.*^[36] concluded that changes in ABMR-associated gene expression correlates with the presence of capillary lesions or of DSAs and may predict graft failure independently of C4d staining. Taken together these observations point to the low sensitivity of C4d for the diagnosis of ABMR and support the addition of novel biomarkers of capillary inflammation and endothelial injury, including natural killer cells and macrophages, for the diagnosis algorithm of ABMR^[37,38]. This recommendation was officially incorporated into the new Banff 2013 diagnostic criteria for ABMR^[39].

The 12th Banff conference on allograft pathology was held in Comandatuba, Brazil in August 2013. The conference led to the following conclusions in the field of ABMR in renal allograft: (1) For acute/active ABMR the following three features must be present for diagnosis, not colon histological evidence of acute tissue injury, evidence of current/recent antibody interaction with vascular endothelium, serologic evidence of DSAs; (2) For chronic/active ABMR the following three features must be present for diagnosis, morphologic evidence of chronic tissue injury, evidence of current/recent antibody interaction with vascular endothelium, serologic evidence of DSAs; and (3) C4d staining without rejection (often accommodation), must include: linear C4d staining in peritubular capillaries, no morphologic lesions by light microscopy and electronic microscopy, no acute cell-mediated rejection.

New techniques involved in rejection diagnosis

Bachelet *et al.*^[40] with a seminal work demonstrated that DSAs detection in kidney allograft biopsy eluates is a

feasible method to predict the graft outcomes. Indeed, patients with intragraft DSAs displayed more severe ABMR pathology and worse outcome than patients with only DSAs in the serum. According to this work the intragraft DSA detection is a new test to dichotomize HLA antibodies into high and low injurious activity^[41].

There are no doubts on the unmet medical need for improvement of diagnostic of renal injury to allow a more personalized therapeutic approach. Therefore, it is believed that the opportunity lies in new technologies such as molecular analysis, as messenger RNA (mRNA) and micro RNA expression from biopsies or even from blood or urine samples^[42].

Two reports from the group of Edmonton in 2013 reported the results of molecular analyses of renal allograft biopsies^[43,44]. The first report aimed to develop a diagnostic test for the T and B cell-mediated rejection by bootstrapping from the pathology.

The main messages of this paper were: (1) A molecular scoring was developed for diagnosis of rejection; (2) A molecular classification is based on selected genes related to immune cells and their activation products; and (3) The study confirmed certain disagreements among pathologists in applying the golden standard histopathology. In two other studies^[45,46] the scoring assessed by the microarray test was validated by the INTERCOM study.

These papers revealed that a previously identified “acute kidney injury signal” early after transplantation was also present in the late kidney biopsies related to late T cell and ABMR, but not to fibrosis.

The multicenter Clinical Trials in Organ Transplantation 04 (CTOT-04) study was designed to investigate whether the urinary-cell mRNA levels encoding immune system proteins implicated in transplant rejection are diagnostic of acute rejection^[47]. By logistic regression the authors correlated a three-gene signature of CD3 ϵ mRNA, IP-10 mRNA, and 18S rRNA levels in urinary cells with allograft rejection. This study offers new insight into the possible use of non-invasive diagnostic and prognostic markers for the acute cellular rejection in kidney allograft.

NEW INSIGHTS FOR PANCREAS AND ISLET TRANSPLANTATION

Transplant activity and graft survival

Pancreas and islet cell transplantation (ICTx) confirmed to be the best treatment for diabetes mellitus type I (T1DM). According the OPTN/SRTR data, the number of pancreas transplants has decreased over the past years, most notably the numbers of pancreas after kidney (PAK) and pancreas transplant alone (PTA)^[48]. Decreased donor pancreas donation rates have been declining since 2005 and the donation rate remains low. The outcomes of pancreas graft are better for simultaneous pancreas-kidney (SPK) transplantation. The challenges of pancreas transplant are reflected in the high rate of re-hospitalization, most occurring within the first six month post-transplant.

Very recent data^[49] confirm the excellent long-term prognosis of SPK transplantation principally in recipients with functioning graft 1-year after transplantation. Patients who receive PTA or PAK grafts have shorter long-term graft survival^[50]. Multiple strategies are aimed to be applied to improve immunologic surveillance and to obtain an early diagnosis of the graft rejection in patients receiving PTA.

An interesting study^[51] documented an improved patient survival rate for recipients with diabetic end-stage renal disease receiving SPK than that receiving kidney transplant alone (KTA). ICTx remains a hot topic. The collaborative islet transplant registry investigators^[52] presented the results of 752 islet allograft recipients with optimal and improving insulin independence rate at 3 years.

Pancreas transplantation for type 2 diabetes mellitus

SPK is widely accepted as an optimal therapeutic option for patients with T1DM and end-stage renal disease, but the indication for patients with type 2 diabetes mellitus (T2DM) is still controversially discussed. Indeed, there is continued uncertainty as to whether to T2DM patients are appropriate pancreas transplant candidates. In an editorial of 2012 Cohen *et al*^[53] reviewed the most recent experience with pancreas transplantation in T2DM.

Gruessner *et al*^[54] summarized the united network for organ sharing (UNOS) and International Pancreas Transplant Registry and reported no differences in the outcomes of patients with T2DM *vs* T1DM. Orlando *et al*^[55] also found equivalent outcomes, regardless of whether the patients were classified as having T1DM or T2DM. Sampaio *et al*^[56] reviewing the UNOS database, reported similar results even if T2DM represented only from 4.1% to 7.4% of diabetic patients transplanted.

More recently, Margreiter *et al*^[57] reported the outcomes of 21 T2DM recipients receiving SPK and 32 T2DM receiving KTA. Patient and kidney graft survival rates were significantly lower for patients with KTA. The multivariate analysis adjusted for donor and recipient age, body mass index and coronary risk factors, showed that the differences did not remain statistically significant. The authors concluded that, according to the selection criteria proposed by other groups^[58], selecting T2DM with an acceptable coronary risk profile and ageing not more than 55 years, is useful to identify those patients that may have a benefit from SPK.

ABMR in pancreas transplantation

ABMR is a recently identified entity. In a recent published paper^[59], risk factors for pancreas ABMR were PTA and race mismatch. The diagnosis should be actively sought using C4d staining and DSAs levels in patients with graft dysfunction.

Preliminary studies have been presented at the already mentioned 2013 Banff conference^[59]. These studies described the potential association of rejection-related vascular lesions with ABMR. Other studies demonstrated that immunostaining can enhance the understanding of pancreas T cell mediated rejection and ABMR even if the

accurate grade and type of rejection rests principally on the systematic evaluation of morphological features on routinely stained sections^[60].

Islet transplantation

ICTx is a modality to treat selected diabetic patients. The “Edmonton Protocol” became a milestone by reporting sustained C-peptide production and high rates of insulin-independence after transplant in T1DM^[61].

Long-term analysis of these results indicates that insulin-independence was not durable and most patients returned to moderate amounts of insulin approximately 5-years post-infusion^[62]. The causes for this islet graft dysfunction are not completely understood, but are likely associated to several factors as the immune rejection, the autoimmunity or the chronic exposure to diabetogenic immunosuppressant^[63].

In the last years relevant progress has occurred testing new immunosuppressant, testing novel devices to provide islets with a safer environments, as well as new transplant sites to overcome the limitations inherent to the current intraportal access^[64-68]. The autoimmunity is a limiting factor to the success of ICTx. In a recent study Takita *et al*^[69], documented an early loss of transplanted allergenic islets despite T cell depletion induction. The authors concluded that the T cell depletion with anti-inflammatory regimen can enhance engraftment and survival; however, autoimmune recurrence by islet auto antibodies, principally GAD65 may limit the results.

The revascularization of transplanted pancreatic islets and the role of the transplantation site is another important issue^[70]. Indeed, pancreatic islets are highly vascularized, which is important for their ability to secrete insulin in response to changes in blood glucose. The islet isolation process interrupts the connections between the islet vasculature and the systemic circulation. As the revascularization of the ICTx is not immediate, allocating cells in proximity to a good vascular supply is essential. A recent study proved the impaired revascularization of pancreatic islets into the liver^[71]. In addition, the portal vein after islets injection undergoes instant blood-mediated inflammatory rejection (IBMIR) which results in an early inflammatory reaction. Therefore, it is essential to avoid this by either identifying a transplant site with minimal interaction with blood or by protecting the vascular grafts from IBMIR^[70].

Among other sites, recent studies documented good results with omentum and muscle. The peritoneum offers an unlimited space for transplanted islets and is an attractive site for concurrent use of encapsulated device to protect the islets. A recent study^[72] suggests the potential for longevity of islets allocated in the peritoneal cavity. Muscle-skeletal sites offer several advantages. They are easy to access, offer substantial space in which to transplant cells and are highly vascularized making them a very useful area. In a recent study, mice islets were successfully transplanted intramuscularly and the authors concluded that the early hypoxia after transplantation could be overcome by co-implantation of polymerized hemoglobin^[73].

Finally, the islet encapsulation has been the issue of a very recent review^[74]. Islet encapsulation allows the protection of this tissue without the use of toxic medications and expanding the donor pool to include animal sources. Before the use of this therapy, there are still issues that need to be resolved as the materials to be used, the shapes and sizes of the capsules and the aspects of bioengineering.

NEW INSIGHTS FOR LIVER

Transplant activity and liver graft survival

According the OPTN/SRTR data, in United States the number of adults who registered on the liver transplant waiting list decreased for the first time since 2002. However, the median waiting time for active wait-listed adult candidates increased, as did the number of candidates removed from the list because they were too sick to undergo transplant^[75]. Graft survival continues to improve, especially for donation after circulatory death livers.

Since the first liver transplantation, short-term survival has improved rapidly; however, long-term attrition rates have not changed similarly^[76]. In 2013 the first publication of European single-center 20-year survival data have been published^[77]. The 20-year patient and graft survival rate of 313 patients has been reported. The 20-year patient and graft survival rates were respectively 52.5% and 46.6%. These results were better than two other single center long-term survivals^[78,79] and also than the 20-year survival published by the European Liver Transplant Registry^[80].

Impaired renal function and re-transplantation had significant impact on patient survival and recurrent diseases. Infections and *de novo* malignancies were the main cause of death. Much work is needed to combat recurrent disease and side effects of immunosuppressants.

The Japanese Liver Transplantation Society analyzed the outcomes of 2224 pediatric patients who underwent living donor liver transplantation^[81]. No donor mortality related to transplant has been reported and the 10 and 20-year patient survival rates were 82.8% and 79.6%, respectively.

Primary disease impacts on the outcomes of liver transplantation (LTx). A recent analysis of OPTN/SRTR^[82] documented an optimal short and long-term survival of LTx for primary biliary cirrhosis; similar good outcomes were reported for primary sclerosing cholangitis, non-alcoholic steatohepatitis and for hepatitis B virus (HBV). The worst results (HR = 1.5-2.4) were reported for hepatitis C virus (HCV) and hepatocellular carcinoma.

More than one-third of listed potential liver recipients in many western and some Asian countries are infected with the HCV. Recurrence of infection with HCV after LTx is associated with accelerated graft loss and diminished patient survival^[83]. Until recently, HCV treatment has been limited to the use of pegylated interferon alpha (Peg IFN) plus ribavirin. In 2012 two direct acting antiviral drugs, boceprevir and telaprevir were licensed by FDA for the treatment of chronic genotype 1 HCV^[84,85]. The use of protease inhibitors (PI) based triple anti HCV

therapy in LTx recipients, is complicated by the known pharmacokinetic effect of the PI on cytochrome P450^[86]. Nevertheless, promising small series of HCV recipients treated by PI based triple therapy have been reported^[87]. Future approaches rely on the possible use of prophylactic neutralizing monoclonal antibodies to HCV^[88].

Ischemia reperfusion injury

IRI is a major cause of morbidity and mortality in LTx. After a transient ischemia, the restoration of blood flow is necessary to restore cellular function, but paradoxically the reperfusion can initiate a cascade of pathways that causes further cellular injury after prolonged ischemia^[89].

The lack of oxygen in hepatocytes during ischemia causes adenosine 3 phosphate depletion and alterations in H⁺, Na⁺ and Ca²⁺ homeostasis that activate hydrolytic enzymes and impair the volume regulation, leading to the swelling of sinusoidal endothelial cells and Kupffer cells (KCs). This fact together with the imbalance between nitric oxide and endothelin production, contributes to the narrowing of the sinusoidal lumen and thus to microcirculatory dysfunction. The activation of KCs releases reactive oxygen species (ROS) and proinflammatory cytokines (TNF alpha and IL 1). Cytokines and chemokines promote neutrophil activation and subsequent release of ROS and proteases. In addition, IL 1 and TNF alpha activate CD4 T-lymphocytes which produce granulocyte-macrophage colony-stimulating factor, IFN gamma and TNF beta. Platelet-activating factor can prime neutrophils for superoxide generation^[90].

Several studies in 2013 evaluated different molecules in attempt to attenuate the damage induced by IRI. The most important studies in this field have been extensively reviewed in the work of Akhtar *et al*^[91]. Attempt to protect IRI may involve several strategies and several pathways^[92-95]. This issue will be described in the therapy chapter.

DSA and acute and chronic liver rejection

The issue of the impact of preformed DSAs on LTx has been a matter of discussion. Early clinical experience showed no differences in patient or graft survival rate^[96-98] and DSAs were thought to be an integral part of tolerance development. Later studies documented that patients transplanted with a positive cross-match had an increased risk of early graft loss^[99-101]. However, since consistent results are lacking, practice has not changed. In 2013, a study from Kaneku *et al*^[102], documented that patients with LTx developing de novo DSAs after transplantation, had significantly lower patient and graft survival rates.

The 2013 Banff conference^[39] stated that currently, recognized acute ABMR, occurs in small percentage of sensitized patients and that DSAs can be associated with more progressive fibrosis and an indolent progressive perivascular and subsinusoidal fibrosis. The conference concludes that high titer IgG3 recipients more often show adverse consequences, whereas exclusively not IgG3/IgG1 DSAs appear in some operationally tolerant recipients weaned from immunosuppression.

New tools for rejection diagnosis

Current liver biopsy is the most frequent used technique to evaluate allograft status and is the gold standard for the diagnosis of the acute rejection after orthotopic liver transplantation (OLT). As already described for the kidney, plasma microRNA is now revealing to be a potential biomarker for acute rejection after OLT^[103,104].

NEW INSIGHTS FOR HEART

Figures, characteristics and trends for heart transplantation

According to the OPTN/SRTR data, in United States the number of heart transplants performed annually continues to increase gradually, and the number of adult candidates on the waiting list increased by 25% from 2004 to 2012^[105]. Heart transplantation (HTx) appears to be more expensive than ventricular assist devices for managing the end-stage heart failure, but is more effective and likely more cost-effective.

By the end of 2013 the data of the Registry of the International Society for Heart and Lung Transplantation (ISHLT) have been published^[106]. Cardiomyopathy in recent years has been the leading cause for HTx, followed by coronary artery disease (CAD). This trend has been particularly higher in Europe and the rest of the world than United States, reaching percentage of 57%-60%. Both recipient and donor age statistically increased, as well as the percentage of patients with pre-transplant panel reactive antibodies in the sera > 10%.

In the recent years a highly significant number of patients bridged to transplantation with mechanical circulatory support (MCS) have been registered. Nevertheless, should be outlined that a better survival rate has been reported for patients not on mechanical support prior transplantation.

A progressive and significant increase of Kaplan Meier survival by ERA was reported except for the last two years. Congenital diseases as primary disease attained the best survival rate while re-transplants attained the worst. Importantly long-term freedom from cardiac allograft vasculopathy (CAV) was higher by ERA and by female gender. The causes of death were stable in the last year with prevalence of graft failure, followed by infections.

In 2013, the ISHLT Registry focused a peculiar study on the relevance of age. Interestingly in the recent years, the graft survival rate was not statistically influenced by recipient age, except 18-39 years compared to 60-69 years. On the contrary donor age had significant impact on the graft survival. CAD was the leading cause of HTx for patients aged 60-69 years (53%).

In the recent years an increase of both donor and recipient age has been registered. The most striking variation for elder patients has been observed as the percentage of patients bridged with MCS. By 2012 almost 40% of patients ageing 60-69 years were on MCS prior to transplantation, while only 15% of patients had similar support by 2006. Leading causes of death for patients ageing 60-69 years were graft failure and infections. The elder patients had also more

malignancies and after 10 years only 50% of patients were free from malignancies.

Mechanical circulatory support

As aforementioned in recent years we observed an impressive advance in MCS devices and, overall, newer MCS devices are smaller and more reliable than the first generation of technological devices. Increasing number of reports conclude that in some cases of heart failure, the devices may be used not only as bridges to transplantation, but also as destination therapies^[107]. A new device, the Heart Ware Ventricular Assist System is a miniaturized implantable continuous flow blood pump and in 332 patients in a pivotal bridge to transplant demonstrated a high 180-d survival rate^[108]. This and other mechanical supports were examined in a recent paper^[109] which led to the conclusion that patients with mechanical support, despite being older and less favorable recipients, spent more time in status 1A and had greater waitlist survival.

In a systematic review, Sutcliffe *et al.*^[110] tried to evaluate the clinical effectiveness and cost effectiveness of last generation MCS as either bridge to transplant (BTT) or alternative to transplant (ATT). The authors concluded that MCS as BTT compared with medical management are effective but with higher cost-effectiveness ratio. MCS as ATT have a reduced cost, but cause reduced quality of life. Considering the wide use of MCS, with the intent to regularize its use, in 2013 ISHLT published the Guidelines for the use of MCS^[111].

Prediction of mortality and cardiac allocation score

As a consequence of the aforementioned variables impacting on heart graft survival, several attempts have been made to evaluate the mortality prediction after heart transplantation. In 2013 the Index for Mortality Prediction after Cardiac Transplantation (IMPACT) score was validated using international data^[112]. This study validated the use of the IMPACT score as a predictor of short- and long-term mortality after orthotopic heart transplantation.

Other scoring modalities, in addition to the IMPACT score, are the Heart Failure Survival Score, the Seattle Heart Failure Model and the Interagency Registry for Mechanically Assisted Circulatory Support. All these scores were evaluated in a Eurotransplant pilot study for predicting waiting list mortality among heart transplant candidates and among transplanted patients^[113]. In non MCS patients all the scores provide accurate risk stratification. The authors conclude that further studies are needed to reveal whether these models should be considered the basis for a new heart allocation policy.

ABMR in heart transplantation

Previous studies have documented that the presence of de novo donor HLA specific antibodies after HTx is an independent predictor of poor survival^[114]. Similarly the detection of Luminex positive DSA in pre-transplant serum is a negative predictor of mortality^[115] and also IgM non HLA antibodies have been identified as a risk for early

allograft failure^[116].

Nevertheless in the last Banff Conference^[39] it was observed that lacking of search for DSAs or C4d staining are limiting factors to identify ABMR in heart transplantation. While biopsies positive for C4d and C3d are strongly associated with DSAs and allograft dysfunction and represent true ABMR, biopsies only positive for C4d are mostly subclinical. On a morphologic basis, is not possible to designate the latter as accommodation *vs* subclinical ABMR. Moreover there is also uncertainty about the management of subclinical ABMR. To this end the American Heart Association will be publishing a scientific statement evaluating clinical and pathological evidence regarding ABMR.

The ISHLT working formulation for the standardization of nomenclature of ABMR in heart transplantation has published a consensus paper by the end of 2013^[117]. As ISHLT itself recognizes is hard to date to make a definitive statement on this issue and there remain numerous challenges and unresolved clinical, immunologic and pathologic questions. Moreover, there is no hard evidence of a direct causality between ABMR and CAV, neither any systematic study of antibody-dependent cellular cytotoxicity as an alternative mechanism linking antibodies to CAV^[39].

Chronic cardiac allograft rejection: new insights

Several papers in 2013 have treated new findings on chronic cardiac allograft rejection. A review by Costello *et al.*^[118] recognized that chronic rejection in the form of CAV is one of the major factors that affect the long-term graft and patient survival. Whereas multiple factors (hyperlipidemia, cytomegalovirus, baseline coronary artery disease) contribute to the development of CAV, immunologic mechanisms play the prevalent role.

Using the intravascular ultrasound (IVUS) to evaluate intimal thickening, some recent studies have validated the use of everolimus (EVR) with reduced-dose cyclosporine (CsA)^[119,120]. These studies documented a similar efficacy of EVR with reduced-dose CsA to Mycophenolate Mofetil (MMF) with standard-dose CsA and a reduced intimal proliferation at 12 mo in *de novo* heart transplant recipients. However, these studies have been criticized^[121] both because IVUS was made only in a subgroup of patients and because IVUS was performed only at 1 year post-transplant.

Finally, the technique of optical coherence tomography has been proposed to evaluate cardiac allograft vasculopathy^[122]. This is a new technique to assess early morphologic changes, but its clinical predictive value remains to be determined.

NEW INSIGHTS FOR LUNG

Figures, characteristics and trends for lung transplantation

In United States lung transplants are increasingly used as treatment for the end-stage lung diseases. Lungs are allocated to adult and adolescent transplant candidates on the basis of age, geography, blood type compatibility and

the Lung Allocation Score (LAS)^[123]. The overall median waiting time in 2012 was 4 mo, and 65.3% of candidates underwent transplant within 1-year of listing. Both graft and patient survival rates have continued to improve; survival rates for recipients aged 6-11 years are better than those of younger recipients. Similarly as for the heart by the end of 2013 the data of the ISHLT Registry have been published also for the lung^[124].

Obstructive pulmonary diseases (COPD), interstitial pulmonary fibrosis (IPF) and cystic fibrosis (CF) are among the most common causes of LuTx. COPD represents one of the most common indications for LuTx and accounts for one-third of all the procedures^[125]. Worldwide a recent analysis of all the recipients reported that 23% had IPF and 3% pulmonary artery hypertension^[126]. LuTx has become an excellent treatment option for patients with CF and bronchiectasis. In these patients survival is more favorable than that seen in patients with COPD and IPF^[127].

In recent years there has been a significant increase of recipient's age (24% ageing 60-65). As a consequence there was an increase of patients transplanted for COPD, for IPF and for re-transplantation. Though the patients with COPD, IPF and re-transplant have the worst survival, an increase of Kaplan Meier survival by ERA was registered. Recently has been reported an increase of bilateral/double LuTx with respect to single LuTx for all the primary diseases. As double LuTx is associated with an improved graft survival rate for any disease, this could be the cause for the improved survival rate observed in recent years.

Among the side consequences of lung transplantation, both a reduction in renal dysfunction and an increase of hyperlipidemia and diabetes has been registered and probably this fact is related to modification in the dose and type of immunosuppressant^[124].

Donor selection and extended criteria donors

The scarcity of suitable donor organs limits lung transplantation^[128]. To overcome this problem, recently there was an increased interest towards an expanded donor pool associated with the techniques aimed to evaluate and improve donor lungs as the availability of *ex vivo* lung perfusion (EVLP). The utilization rate of these lungs changed from less than 15% to 50%. It is now quite clear that many of the historical factors used to define a lung as "Extended" do not actually produces significantly worse outcomes.

In a review of the UNOS database^[129], the outcomes after LuTx using donors aged 55 to 64 years, were similar to those observed with standard donors. In this review only the donors aged more than 65 years were associated with the decreased intermediate-term survival. In Eurotransplant in 2013 the Hannover center reported its results utilizing lungs turned down for donor-related medical reasons by 3 centers. The authors obtained excellent graft survival similar to the standard lungs and concluded that the rescue allocation donor lungs may be used safely and therefore salvaged for the donor pool^[130].

New findings on recipients and LAS

The relevance of size-matching has been evaluated in

an extensive study based on evidence-based reviews^[131]. Unfortunately the authors conclude that the evidence base that informs the decisions regarding lung size mismatching is limited and composed primarily of small studies with heterogeneous groups of patients.

Currently data are lacking to give the surgeons robust guidelines to conduct decision making for size matching of donors and recipients. Among the pre-transplant variables that affect the survival after LuTx, markers of nutritional status are associated with poorer recipient survival. A recent paper^[132] examined several variables associated with the nutrition, including body mass index, body surface area, albumin levels, total proteins and immunoglobulins. Although no nutritional variables were found to be associated with major post-operative complications or infections, a low serum albumin (< 3 mg/dL) was associated with increased risk of death. Even if the results of this study differ slightly from others studies^[133]; the body of literature to date suggests that the nutritional status may affect post-transplant outcomes.

The LAS was developed in 2005 to reduce the mortality on the waiting list, to prioritize candidates basing on urgency, to minimize the role of geography and to maximize the transplant benefit. In prioritizing patients with the most urgent status, a new controversy has come into the forefront: whether or not the increased number of critically ill recipients maximizes the transplant benefit. Despite the controversy, the LAS system is an improvement compared with the traditional first-come, first-served system and it has been adopted by UNOS and Eurotransplant^[134]. A recent review of the UNOS data^[135] concluded that social disparities in lung transplantation have decreased with the implementation of LAS; however, gender disparities (in favor of men) may have actually increased in the LAS ERA.

Primary graft dysfunction, ABMR and chronic allograft dysfunction

Primary graft dysfunction (PGD) is a syndrome encompassing a spectrum of mild to severe lung injury that occurs within the 72 h after LuTx. In addition, PGD has a significant impact on the short and long-term outcomes^[136].

The pathogenesis of PGD is complex and influenced by donor, recipient, technical factors and by different combinations of all the above. PGD is driven by an inflammatory response as well as by immunological (both innate and cell mediated) processes^[137]. Several strategies have been investigated to prevent and treat PGD^[138]. These strategies will be discussed in the therapy chapter.

Allograft rejection is a major cause of a limited survival rate in LuTx. Moreover, the acute rejection represents the principal risk factor for chronic rejection^[139]. Acute cellular rejection (ACR) is defined as a perivascular or peribronchiolar lymphocytic infiltrates primarily diagnosed by bronchoscopic transbronchial biopsies^[140]. ACR involves several T-cell subtypes and several cytokines.

Data suggest a correlation between acute rejection and effector memory T cells in LuTx and the measurement of peripheral blood CD8+ effector memory T-cells before

LuTx may define the patients at high risk for ACR^[141].

The study of Krustup *et al.*^[142] documented the association between the distribution of Tregs in the transbronchial biopsies and the level of FoxP3 mRNA in the bronchoalveolar lung fluid (BALF). This indicates that Tregs may play a role in the cellular processes that affect ACR and that looking for FoxP3 mRNA in BALF is a reliable non-invasive method for evaluating the number of Tregs in lung tissue.

Higher values of CXCL10 (IP-10) in BALF are associated with ACR in LuTx suggesting a potential mechanistic role in the pathogenesis of ACR^[143]. These results suggest that therapeutic strategies to inhibit CXCL10 (IP-10) and/or its cognate receptor (CXCR3) warrant investigations to prevent and/or treat the ACR in LuTx.

Some retrospective studies conducted and published in 2013 highlighted the relevance of ABMR in LuTx. In one study^[144] a clear association between DSAs, ABMR, ACR, bronchiolitis obliterans syndrome (BOS) has been documented. Another study^[145] identified ABMR in 21 recipients basing on the presence of HLA-DSAs, the histological evidence of acute lung injury, C4d deposition and clinical allograft dysfunction. In this study the majority of patients who recovered from ABMR, developed chronic lung allograft dysfunction (CLAD) during the follow-up.

Due to the relevance of the syndrome, the Pathology Council of the ISHLT elaborated the Consensus points for pathologic diagnosis of pulmonary ABMR^[146]. The conclusions were: (1) The diagnosis of pulmonary ABMR requires a multidisciplinary approach that includes the presence of clinical allograft dysfunction, circulating DSAs and pathologic findings; (2) The histopathology findings in ABMR are non-specific patterns of injury that can be seen also in disorders such as severe ACR, infection, graft preservation injury and drug reaction; and (3) Positive capillary C4d staining should be always reported.

The last Banff conference^[39] reviewed the Pathology Council survey and added that the early detection of DSAs following LuTx and the systematic monitoring with sensitive solid-phase platforms are recommended^[147]. The overall conclusions revealed that to date survival is poor after ABMR but may improve with the rapid clearance of the antibodies^[145].

Important unanswered questions include: (1) How to grade graft dysfunction; (2) What constitutes a significant mean fluorescent intensity of DSAs; (3) How to manage the patient in whom there is discordance between the criteria enumerated; and (4) What's about the non-HLA targets, principally because, according many authors, the BOS is the result of humoral response against non-HLA molecules^[148].

CLAD continues to be the major limitation to long-term survival^[149]. Its pathogenesis is complex and involves both alloimmune and non-alloimmune pathways. In particular, acute damage to the allograft, including episodes of acute rejection, PGD, cytomegalovirus (CMV), pneumonitis, gastro esophageal reflux and early and late new-onset diffuse alveolar damage have all been shown to increase the risk of CLAD^[150].

BOS, characterized by obstructive physiologic changes,

is the conventional form of CLAD. Increasing evidence, however suggests that CLAD is a heterogeneous condition and that BOS is not the only form of CLAD. While BOS itself has been recently redefined as neutrophilic reversible allograft dysfunction (NRAD)^[151], Sato *et al.*^[152,153] recently identified a type of CLAD who showed restrictive physiology and peripheral lung fibrosis and named this condition "restrictive allograft syndrome" (RAS). The prognosis of RAS is poor and more severe than that of NRAD.

As already mentioned the pathogenesis is multi-factorial and recently has been documented that acute rejection, lymphocytic bronchiolitis, colonization with *Pseudomonas*, infection and BALF eosinophilia and neutrophilia are risk factors for both RAS and NRAD^[154]. Moreover, immunologic factors as complement activation^[155] and the defensins have been implicated in the pathogenesis of CLAD^[156].

NEW INSIGHTS ON IMMUNOSUPPRESSIVE THERAPIES IN SOLID ORGAN TRANSPLANTATION

This chapter may be divided into two paragraphs: (1) Old drugs recently revised and used in new strategies; and (2) New drugs recently introduced on the market or still waiting for their approval.

Old drugs recently revised and used in new strategies

The concept that the chronic loose of renal function after kidney transplantation (KTx) should be ascribed to chronic renal calcineurine inhibitors (CNIs) nephrotoxicity, led to a number of trials attempting to avoid or withdraw CNIs from the maintenance immunosuppression therapy.

With the exception of few trials all these attempts documented that to date is not yet the time to give up with CNIs^[157]. Moreover, in 2013 a meta-analysis^[158] has not documented a favorable effect of CNIs reduction on kidney function in HTx.

Many trials of CNIs reduction have been made thanks to the use of mammalian target of rapamycin inhibitors (mTORIs), a class of drugs devoid of CNIs side-effects. Overall an analysis of 139370 United States kidney transplant recipients documented that the complete substitution of CNIs with mTORIs was associated to a greater risk of allograft failure and death^[159].

The use of mTORIs in LTx led to contradictory results. In a phase II prospective randomized trial^[160] the use of sirolimus with reduced dose of tacrolimus (TAC) in the de novo liver transplant recipients was associated with higher rates of graft loss, deaths and sepsis when compared to the use of the conventional dose of TAC.

In the recent H2304 trial^[161,162] liver transplant patients randomized to EVR with TAC elimination showed strikingly good renal function at 2-year post-transplant, but this treatment group was terminated due to a higher rate of acute rejections. However, there was no significant

difference between the EVR and reduced TAC *vs* TAC control group^[163]. The study Preservation of Renal function in liver Transplant recipients with Certican Therapy (PROTECT)^[164] documented that an EVR-based CNI-free immunosuppression is feasible following LTx and the patients benefit from sustained preservation of renal function when compared to patients on CNIs, for at least three years.

The discrepancies between the results of H2304 and PROTECT studies could be explained by the use of IL-2 receptor antibody only in the latter study and in the abrupt TAC withdrawal in the former.

The contradictions in the use of mTORIs in LTx have been examined in an editorial of Levitsky *et al.*^[165]. Probably like any other drug with a narrow therapeutic window, mTORIs must be used in the right amount, right time period and right patient. Right amount is without a loading dose and targeting moderate trough levels. Right time is neither too early nor too late after LTx. The right patient is the one who is at high risk to develop nephrotoxicity.

Several studies document the attenuation of cardiac allograft vasculopathy by mTORIs. A study from Matsuo *et al.*^[166] documented the usefulness of sirolimus in the case of early initiation. As aforementioned, the recent most important contributions in this field are the Eisen *et al.*^[119] and Kobashigawa *et al.*^[120] studies.

They documented the efficacy of EVR with reduced-dose CsA, similar to MMF + standard dose CsA. Patients treated by EVR had reduced intima proliferation. Recently the use of mTORIs in the treatment of lung transplant recipients is an area of active investigation^[167,168]. Newer researches involving the use mTORIs or antimetabolites have been made in the treatment and prevention of BOS^[169,170]. In a recent review^[171], Borro highlights that one of the advantages in LuTx is the administration of the treatments *via* the inhalator route.

A randomized, prospective study of inhalator CsA *vs* placebo documented significant improvements concerning survival and BOS free interval^[172]. Inhalator corticosteroids have been suggested in the lymphocytic bronchiolitis, based on the possible reduction of the airway inflammatory markers^[173].

Immune modulating and beneficial effect in LuTx have been documented for the statins and Azithromycin. Concerning statins, some groups have considered adding such treatment on a systematic basis in the patients with suspected or confirmed BOS^[174]. Principally in patients with an increased bronchoalveolar lavage neutrophilia, azithromycin could prevent BOS, most likely through its interactions with the innate immune system^[175].

The finding of the relevance of DSAs in determining ABMR and reduced graft function for any transplanted organ led to search for new strategies in organ immunosuppression. A systematic review^[176] on the induction therapy in HTx concluded that acute rejection might be reduced by IL-2R antibodies compared with no induction and by the antithymocyte globulin (ATG) compared with IL-2R antibodies. Similarly, the

depleting antibody induction has become the mainstay of immunosuppression in pancreas TX^[177].

In KTx the use of ATG is associated with a significant reduction of DSAs and ABMR^[178]. The Alemtuzumab induction therapy obtains similarly good results in a systematic review^[179]. Further induction trials in the attempt to prevent ABMR with rituximab are ongoing, including the Rituximab Induction in Renal Tx (ReMIND) trial (ClinicalTrials.gov No. NCT01095172)^[180,181]. No result has been obtained with Rituximab in the treatment of ABMR as reported from a phase III multicenter, randomized, placebo-controlled trial (RITUX ERAH)^[182].

New drugs recently introduced in the market or still waiting for approval

Prevention and treatment of ABMR: Eculizumab, the humanized anti C5 antibody is among the new drugs recently used in the prevention of the ABMR in KTx. Its efficacy was recently assessed in one study^[183]. There is an ongoing, multicenter, international, randomized trial testing the role of eculizumab that may clarify its utility (NCT00670774)^[184].

Limited clinical trial evidence suggests that the proteasome inhibitor Bortezomib may be useful to treat the ABMR following KTx^[185]. Agents targeting the B activating factors belonging to the TNF Family (BAFF) pathway which co-stimulates B cell survival and expansion are also in the clinical development as ataccept and belimumab^[186].

A further possibility in the field of ABMR is complement inhibition by C1-esterase inhibitors. A trial studying the safety and tolerability of the C1 inhibitor therapy in the prevention of the acute rejection is now ongoing (Clinical Trials gov NCT01134510).

New drugs in KTx: Belatacept, a fusion receptor protein that blocks the co-stimulation pathway CD80/CD86-CD28, was recently approved for the prevention of acute rejection in KTx. In 2013 two papers reported the results at 5 years of immunosuppression with belatacept + MMF and steroids respect to standard CsA maintenance immunosuppression^[187,188]. Continued treatment with belatacept was associated with a consistent safety profile and sustained improvement in renal function *vs* CsA overtime.

In a smaller study Kirk *et al.*^[189] documented the feasibility of an immunosuppressive therapy in KTx with belatacept only, without maintenance steroids or CNIs after alemtuzumab induction. Another co-stimulation pathway is the CD40/CD40L pathway. Humanized anti CD40 antibodies prevented the acute rejection and prolonged the renal graft in non-human primates. In addition, these anti-CD40 antibodies appear safe and effective as maintenance immunosuppressive therapies^[190,191]. To date 5 monoclonal antibodies directed against CD40 have been studied for different diseases including KTx (ClinicalTrials.gov NCT01780844).

Alefacept is a recombinant LFA3/IgG1 fusion protein that reduces the number of memory T cells. After its

successful use in psoriasis, a recent study evaluated the efficacy of alefacept when combined with TAC, MMF and steroids in renal transplant patients^[192]. Six-month efficacy, safety and tolerability were similar to control group, but the trial was too short to draw conclusions.

Janus kinase (JAKs), are a cytoplasmic tyrosine kinases that participate in the signaling of a broad range of cell surface receptors. JAK3 inhibition by tofacitinib in KTx trials in humans^[193,194] have demonstrated tofacitinib to be non inferior to CsA for rejection rates and graft survival, however there was a trend towards more infections.

Sotrastaurin (AEB071) is a small molecular weight immunosuppressant that blocks the early T cell activation through selective inhibition of protein kinase C, crucial for IL-2 and interferon gamma production. In a phase II trial^[195] sotrastaurin at a dose of at least 200 mg/d + reduced TAC had comparable efficacy to mycophenolic acid (MPA) in prevention of rejection. In another phase II study^[196] sotrastaurin + everolimus compared to CsA + EVR had higher efficacy rates failure.

New drugs in pancreas Tx and ICTx: In pancreas Tx, after induction therapy the most widely used maintenance protocols are based on TAC and MMF with steroid withdrawal^[197]. Considering the recent documented negative impact of DSAs on pancreas Tx, whether promising novel agents such as sotrastaurin, tofacitinib, belatacept, bortezomib or eculizumab will prove to be beneficial for pancreas Tx requires further investigations.

A long-term insulin-independence after ICTx was documented in 10 patients adding efalizumab or belatacept to the standard immunosuppression^[64]. In another study^[65] efalizumab was compared to belatacept and has been documented that efalizumab increases percentages of the circulating Tregs and profoundly suppresses T-cell reactivity, thus promoting the transplantation tolerance.

Combining anti-inflammatory biologics to maintenance immunosuppression has led to improved success rate. Naziruddin *et al*^[66], adding etanercept (TNF alpha antagonist) to immunosuppression obtained protection from inflammatory reaction during the peritransplant period. The same authors obtained an even better protection adding Anakinra (IL-1 beta blocker) to Etanercept^[66]. Another group obtained excellent results adding Reparixin (CXCL8 inhibitor) to the immunosuppressive therapy^[67,68].

The stabilization of Glucagon-Like-Peptide-1 (GLP-1) by inhibiting Dipeptidyl Peptidase IV by sitagliptin increases beta cell mass by modulating vascularization^[198]. To date two official trials are ongoing on the effect of sitagliptin (NCT00853944 and NCT01186562).

New drugs in LTx: In liver transplantation new drugs have been principally used to protect the IRI. Attempt to protect the IRI may involve several strategies and several pathways^[92-95]. Elias-Miro *et al*^[92] evaluated antioxidant strategies to reduce the oxidative stress. The positive Pentoxifylline effect seems to be related to the inhibition of

TNF alpha according Genoves *et al*^[93].

Tiriveedhi *et al*^[94] found a protective effect of Bortezomib on IRI. This proteasoma inhibitor effectively attenuates the IRI by inhibiting the matrix metalloproteinase and the chitinase 3-like 1 (YLK-40) both involved in the extracellular matrix deposition and fibrosis principally in steatotic livers. The complement pathway is also involved in the IRI and a recent and promising study in the mice^[95] documented that the C1-esterase inhibitor administration attenuates the liver injury compared to controls.

New drugs in LuTx: New drugs in the field of LuTx are represented by pirfenidone and the C1 esterase inhibitor. Pirfenidone, a small synthetic non peptide molecule demonstrated a potent antifibrotic effect by inhibiting the transforming growth factor beta (TGF beta) and TNF alpha, important mediators of fibrosis and inflammation. Its usefulness has been principally suggested in the lung transplant patients with RAS^[199].

Over the last few years, the development of innovative techniques such as EVLP or the refinement in the artificial support methods as Extracorporeal Membrane Oxygenations also contributed to treat and redefine the outcomes of patients with PGD. A very recent study by Sommer *et al*^[138] reported a trial with C1-esterase-inhibitor in patients affected by severe PGD. The one year survival was significantly higher than that of not treated patients.

NEW INSIGHTS ON TRANSPLANT TOLERANCE

One of the hallmarks of the adaptive immune system is its ability to recognize a vast number of different antigens. This ability is a consequence of the large lymphocyte repertoire, in which each cell has a different antigen receptor generated by the process of somatic recombination. This process is able to produce an estimate of 10¹⁵ different lymphocyte clones, each with a different antigen receptor that can hypothetically recognize any naturally occurring structure^[200]. Since the somatic recombination is a random process, it generates T cell clones that can recognize self-structures or self-peptides (auto antigens). The mechanism used by the immune system in order to avoid a possible harmful immune response against an individual's own cells and tissues, is known as the immune tolerance and can be classified into central and peripheral tolerance.

Immune tolerance in transplantation is defined as a specific absence of a destructive immune response to a transplanted tissue without immunosuppression. Operative criteria are the complete withdrawal of immunosuppression followed by no evidence for rejection for the transplanted organ for over one year. In humans is characterized by specific *in vitro* non-responsiveness to the donor.

Induction of tolerance differs according the transplanted organ. Indeed, although up to 20% of liver transplant recipients may be successfully withdrawn from immunosuppression^[201]; operational tolerance to renal allograft appears to be much

less frequent. In a recent review, Ruiz *et al.*^[202] reviewed the new strategies to induce the long-term acceptance to organ transplantation. These include: (1) Mixed chimerism as a strategy to induce allograft tolerance; (2) Dendritic cells and Regulatory Macrophages; (3) Exosomes and Phagosomes as tools for alloantigen delivery; (4) Apoptotic cells; (5) Regulatory T cells; and (6) Mesenchymal Stromal/Stem cells.

In the recent American Society of Transplantation (AST) Cutting Edge of Transplantation meeting, held in Arizona (US) February 13th-15th 2014, the best approaches to induce renal allograft tolerance have been reviewed. They are principally two: (1) Tolerance through induction of durable chimerism. In HLA disparate patients the protocols to date principally used are the Massachusetts General Hospital and the Northwestern University protocols; and (2) Immunomodulation through use of donor hematopoietic stem cells, as the Northwestern University protocol.

Mixed chimerism is defined as the coexistence of donor and recipient hematopoietic cells after allogeneic bone marrow transplantation (BMT). To be considered mixed chimerism, donor cells in the blood must represent more than 1% of the total cells. To induce a state of mixed chimerism, it is necessary to perform a conditioning treatment in order to allow the donor bone marrow acceptance. Currently used mixed chimerism protocols induce robust donor-specific tolerance and allow long-term acceptance of fully mismatched skin grafts in murine models^[203].

Recently Kawai *et al.*^[204] reported the results of a study of combined kidney and bone marrow transplantation without maintenance immunosuppression. The conditioning regimen consisted in cyclophosphamide, thymic irradiation, antiCD20 monoclonal antibody and an 8 to 14 mo course of CNIs.

The major problems encountered with these protocols have been “the engraftment syndrome” which causes transient renal dysfunction^[205] and the occurrence of low levels of DSAs after discontinuation of immunosuppression. To overcome the engraftment syndrome, the authors have considered the use of low-dose total-body irradiation rather than cyclophosphamide as preconditioning treatment. DSAs occurrence caused an increase of anti CD20 administration.

As myeloablative conditioning is not ethically accepted due to the high risk involved in this type of conditioning, non myeloablative conditioning has emerged as an alternative to induce tolerance through mixed chimerism. Using a simultaneous bone marrow and kidney transplantation and a preconditioning protocol consisting in the co-stimulatory blockade with anti CD154 antibody, Kawai *et al.*^[206] and Wekerle *et al.*^[207] achieved the establishment of mixed chimerism in non-human primates. Later on, Kawai *et al.*^[208] reported tolerance induction using pharmacological immunosuppression and thymic irradiation. The main obstacle remains the presence of the memory T cells that can cross-react with alloantigens^[209].

Other immunomodulatory cells with a high potential in future therapies in transplantation are hematopoietic mesenchymal stem cells (MSCs). It is well known that

bone-marrow derived MSCs have the capacity to migrate to inflammatory sites and regulate the function of most immune cells through direct contact and/or by cytokine secretion^[210].

Leventhal *et al.*^[211] developed an approach using a bioengineered mobilized cellular product enriched for hematopoietic stem cells (HSC) and tolerogenic CD8 positive/T cell receptor (TCR) γ graft facilitating cells (FCs), combined with non-myeloablative conditioning. This allows the engraftment, a durable chimerism, and the tolerance induction in highly mismatched related and unrelated donor-recipient pairs.

The same author^[212] reported in 2013 an intermediate-term follow up of this phase II trial. All 20 patients demonstrated donor specific hypo-responsiveness and were weaned from full-dose immunosuppression. Complete immunosuppression withdrawal at 1 year was successful with durable chimerism in the majority of patients. No graft *vs* host disease or engraftment syndrome has been reported. In all the cited studies a predictive biomarker for success *vs* failure in weaning immunosuppression has not been reliably identified and validated so as to be used as a tool to discontinue immunosuppression.

Leventhal *et al.*^[213] documented that durable chimerism predicts the outcome. Moreover, the immune/inflammatory gene expression in the peripheral blood and urine were differentially down regulated between tolerant and non tolerant recipients. As aforementioned memory T cells (T_m) represent a major barrier for immunosuppression and tolerance induction after solid organ transplantation. Taking into consideration the critical role of the intrinsic apoptosis pathway in the generation and maintenance of T_m, Cippà *et al.*^[214] developed a new concept to deplete alloreactive T_m by targeting B Cell Lymphoma-2 (Bcl-2) proteins. The small-molecule Bcl-2/Bcl-XL inhibitor ABT-737 efficiently induced apoptosis in alloreactive T_m *in vitro* and *in vivo* and prolonged skin graft survival in sensitized mice. Since Bcl-2 inhibitors yielded encouraging safety results in cancer trials, this novel approach might represent a substantial advance to prevent the allograft rejection and induce tolerance in sensitized recipients.

The mechanisms above mentioned to induce tolerance are almost the same for the liver, even if the liver has particular tolerogenic properties that allow its being spontaneously acceptable in some animal species. The liver structure is considered to favor a tolerogenic environment. Indeed several studies demonstrated that the liver capacity to induce tolerance partly results from the *in situ* T-cell activation. The hepatocytes, as non-professional antigen presenting cells (APCs), may play key roles in regulating the immune responses and facilitating tolerance induction^[215]. Warren *et al.*^[216] documented that the intrahepatic lymphocytes and the circulating naïve CD8+ cells could interact with the hepatocytes by means of cytoplasmic extensions capable of going through the liver sinusoidal endothelial cells fenestrations. This local activation of T cells by the hepatocytes provides the latter with a significant role as APCs and induces tolerance development in the liver^[217]. The peripheral tolerance

mechanisms also play a role in liver graft spontaneous tolerance. As for kidney, also for the liver the most significant mechanism in the tolerance induction is the chimerism^[218]. In humans BMT-induced mixed chimerism has been shown to confer the acceptance of donor liver allograft without long-term immunosuppression. However, recipients must be able to withstand the conditioning regimens that allow donor stem cell to engraft.

NEW INSIGHTS ON MAJOR COMPLICATIONS IN TRANSPLANTED PATIENTS: INFECTIONS AND CANCERS

Infections

Infections post solid organ transplantation (SOT) is one of the more important complications. In 2013 many papers have been published on this topic. Among these, the most relevant, in our opinion are: (1) The publication of the third Edition of the American Society of Transplantation on Infectious Disease Guidelines^[219]; (2) the publication of the Public Health Service (PHS) Guidelines for Preventing Transmission of Human Immunodeficiency Virus (HIV), HBV and HCV through organ transplantation^[220]; (3) the International Consensus Guidelines on the Management of CMV in SOT^[221]; and (4) an overview on CMV and the Herpes Viruses in transplantation^[222].

Two main factors increase the risk for transplanted patients for infections following transplantation: (1) Risk related to the continuous expanding pool of marginal donors; and (2) Risk related to the requirement to increase immune suppression to treat rejection after SOT. In particular the use of antilymphocyte preparations and many of an increasing diverse list of biologic agents have been associated with an enhanced risk of infection^[223].

Overall the risk factors that predisposes to infections in the recipients of SOT may be categorized as being present before transplant within the recipient and those secondary to intraoperative and post-transplant events^[224]. Organ transplant recipients are at risk of acquiring pathogens from donors with active or latent infections at the time of the procurement. Examples of pathogens associated with expected donor-derived infections include CMV, Epstein Barr Virus and Toxoplasma. Of greater concern is the development of unexpected donor-derived infections from a growing number of pathogens, including Mycobacterium tuberculosis, Histoplasma, West Nile virus, HBV, HCV and HIV.

Although OPTN policy requires that all potential deceased organ donors are screened for HIV, HBV and HCV by serology, no current policy requires the use of nuclear molecular acid testing (NAT) for donor screening. In 2013 an electronic survey was sent to 58 Organ Procurement Organizations (OPOs) in the United States to assess the current screening practices^[225]. All OPOs performed the required serology screening, even if only

52% performed NAT for HIV and HCV. Moreover, respect to a previous survey made in 2008^[226], the number of OPOs performing NAT has increased and more OPOs are now testing all donors.

In 2013 the PHS published new Guidelines for reducing HIV, HBV and HCV transmission through organ transplantation^[220]. These Guidelines superseded the 1994 PHS Guidelines^[227]. Most significant changes are: (1) Expanding the Guideline to include HBV and HCV in addition to HIV; (2) Using factors known to be associated with an increased likelihood of recent HIV, HBV or HCV infection; and (3) Limiting the focus to organs and blood vessel conduit recovered for organ transplantation because the FDA implemented more comprehensive regulations for human cell and tissue products^[228].

These guidelines include 34 recommendations on risk assessment of living and deceased donors; informed consent discussion with transplant candidates; testing of recipients' pre and post transplant, collection and/or storage of donor and recipient specimens and tracking and reporting of HIV, HBV and HCV.

Studies on specific pathogens

The human BK polyomavirus is the major cause of polyomavirus-associated nephropathy (PyVAN). Because effective antiviral therapies are lacking, screening kidney transplant patients for BKV replication in urine and blood has become the key recommendation to guide the reduction of immunosuppression in patients with BKV viremia. Retransplantation after PyVAN is largely successful, but requires close monitoring for recurrent BK viremia^[229].

Sood *et al.*^[230] evaluated the relationship of pre-transplantation BK virus-specific donor and recipient serostatus to post-transplant BKV infection. Overall infection was highest in the D+R-group and lowest in the D-R-group. BKV serostatus may be used to risk stratify patients for post-transplantation infection.

CMV remains one of the most common complications affecting SOT, with significant morbidity and occasional mortality. In addition to the direct effects of CMV infection and disease, there are indirect effects, both general and transplant specific, which may significantly impact the outcomes.

An international panel of experts was convened by late 2012 to revise and expand evidence and expert opinion-based consensus guidelines. The reports of such recommendations have been published in 2013^[221]. Viral culture of blood or urine has a very limited role for the diagnosis of the disease. Histology/immune-histochemistry is the preferred method for diagnosis of tissue-invasive disease. Quantitative nucleic acid amplification testing (QNAT) is preferred for diagnosis, decision regarding pre-emptive therapy and monitoring response to therapy. If QNAT is not available, antigenemia is an acceptable alternative.

Both universal prophylaxis and pre-emptive strategies are viable approaches for the prevention of CMV disease. For D+R- the use of either prophylaxis or pre-emptive therapy after kidney and liver transplant are recommended. For

D+R- the use of prophylaxis over pre-emptive therapy after heart and lung Tx is recommended. When a pre-emptive therapy strategy is used, it is recommended that the centers develop and validate their local protocol^[231]. For non-severe CMV disease, Valganciclovir or intravenous Ganciclovir are recommended as first line treatment, while dose reduction of immunosuppressive therapy should be considered in severe CMV disease.

CMV vaccines are in preclinical, phase I and phase II trials^[232,233]. The primary goal of a CMV vaccine should be to prevent or to modulate CMV replication and/or CMV disease. Herpes viruses infect most animal species. Infections due to the eight human herpes viruses (HHV) are exacerbated by immunosuppression in SOT. The special features of the herpes virus life cycle include the ability to establish latent, non-productive infection and the life-long capacity for reactivation to productive lytic infection. Interactions between the latent virus and the immune system determine the frequency and severity of symptomatic infection. In an overview Fishmann^[222] reports how the immunologic and cellular effects of herpes virus infections contribute to risk for the opportunistic infections and the graft reactions. Among the most important advances in transplantation are laboratory assays for the diagnosis and monitoring of herpes virus infections and antiviral agents with improved efficacy in the prophylaxis and therapy.

HCV infection is common in SOT recipients and is a significant cause of morbidity and mortality after transplantation. The severity of HCV infection in liver transplantation has been already discussed in the liver chapter. Carbone *et al.*^[234] reviewed the extent of the problem in donors, kidney, heart and lung transplant candidates.

In HCV-infected kidney allograft recipient, the progression of fibrosis should be evaluated serially. Transplantation of kidneys from HCV positive donors should be restricted to HCV positive recipients. HCV antiviral therapy should be considered for all HCV-RNA positive kidney transplant candidates. The impact of HCV infection on survival in heart and lung transplantation is unclear but even assuming a worse survival in those receiving HCV-infected organs, it has not been evaluated whether they do better or worse than those remaining on the waiting list.

Cancers

Malignancies after SOT are divided into three chapters: donor transmission of cancer, recipients with prior cancer and general epidemiology of cancers after SOT.

Donor transmission of cancers: Xiao *et al.*^[235] reviewed all case reports, case series and registry studies that described the outcomes of the kidney transplant recipients with donor cancer transmission published up to December 2012. The most common transmitted cancer types were renal cancer, followed by melanoma, lymphoma and lung cancer. Overall the risk of donor transmission of cancer appears low, but there is a high likelihood of reporting bias. The findings of this review support the current recommendation for

rejecting organs from donors with a previous history of melanoma and lung cancer, but suggest that the use of donor kidneys with a history of small, incidental renal cell cancer may be reasonable.

At the 2013 American Transplant Congress (ATC), Desai *et al.*^[236] analyzed data from 30000 recipients of SOT from more than 14000 donors in the National Transplant Registry (NTR) in the United Kingdom to determine whether the risk of cancer transmission from organ donors could be eliminated. They found a very low rate of donor-origin cancer: only 0.6%. The risk of cancer transmission cannot be eliminated because the presence of cancer was not known at donation. This finding is useful to obtain an informed consent for prospective recipients, but in transplants other than kidney and pancreas, the benefits should be planned against the risk of remaining on the waiting list.

In another study the same group looked at donor transmission in a different way, linking donor data to the cancer registries, to determine the risk for donor transmission to the recipients analyzing more than 17000 donors^[237,238]. More than 200 (about 1.5%) had a cancer history. Although 61 of these donors were at high risk for transmission, none transmitted their cancer to any of the recipients. These data raise the question about whether we are being too strict and losing potential donors. To put this in context, the death rate on the waiting list is 5% to 15% per year compared with this very low rate of donor transmission of cancer.

At 2013 ATC, Engels *et al.*^[239,240] analyzed data from the SOT registry in the United States to link donor organs to 15 cancer registries. They concluded that recipients of donors with the cancer did not have significantly increased incidence of cancer compared with the recipients whose donors did not have cancer.

Risk of recurrence of preexisting cancer in organ recipients: Again Desai *et al.*^[241] analyzed data from NTR in United Kingdom on the issue of the recurrence of a preexisting cancer in an organ transplant recipient. They identified 64 (1.32%) recipients with a history of cancer diagnosed before organ transplantation.

Five recipients developed cancer recurrence and the rate of recurrence within 10 years was 11.9%. This study is interesting because data on this topic are sparse, and it's increasingly become a problem for nephrologists as the ESRD population ages and the burden of co morbidity in KTx candidates is increasing. Although this is a small cohort, the data are useful because this is one of the only contemporary studies of cancer recurrence risk in SOT recipients.

De novo post-transplant malignancies

De novo post-transplant malignancies (PTM) are a serious complication post-transplantation. In an analysis of the US National Transplant Data, Sampaio *et al.*^[242] analyzed 200000 recipients of kidney, liver, heart and lung. The PTM incidence was 8.03, 11, 14.4 and 19.8 in KTx, LTx, HTx and LuTx respectively. The PTM recipients were older,

mostly white and males in all SOTs.

A cohort study was conducted in Australia using population based, liver and cardiothoracic registries^[243]. During a median 5-year follow-up, the risk of any cancer in the liver and cardiothoracic recipients, was significantly elevated compared to the general population (Standardized Incidence Ratio = 2.62). An excess risk was observed for 16 cancer types, predominantly cancers with a viral etiology. The adjusted HR for any cancer in all recipients was higher in heart compared to liver (HR = 1.29). Understanding the factors responsible for the higher cancer incidence in cardiothoracic compared to liver recipients has the potential to lead to targeted cancer prevention strategies in this high risk population.

Two interesting presentations at the ATC 2013 focused the association between the development of a skin cancer and the subsequent development of a solid organ tumor. Cho *et al*^[244] analyzed data from OPTN/UNOS database and compared the incidence of solid tumors in organ recipients with and without melanoma skin cancer (NMSC). Developing a skin cancer was a risk factor for developing a solid tumor: 9.4% in those who developed a skin cancer *vs* 3.3% in those who did not.

A very similar study was conducted in Australia. McDonald *et al*^[245] analyzed the data from Australia and New Zealand Dialysis and Transplantation (ANZDATA). They found that having a NMSC increased the risk of other cancers by 1.2%. These studies are interesting because skin cancers may be a useful tool to identify people at higher risk for developing other cancers.

The International Transplant Skin Cancer Collaborative (ITSCC) and its European counterpart: Skin Cancer in Organ Transplant Patients Europe (SCOPE) held by the end of 2012 a joint meeting that has been recently published^[246].

The cutaneous squamous cell carcinoma (CSCC) incidence has been previously ascribed to immunosuppressive therapies. The decreased immunosurveillance by innate and adapted immune cells has been investigated and the specific role of macrophages. The direct effect of immune suppression on keratinocyte development has been postulated as well. Because of the need of CSCC epidemiology studies, was outlined an international collaboration between ITSCC and SCOPE to prospectively study CSCC in transplant patient.

CONCLUSION

In few fields of human medical knowledge, the science is so rapidly evolving as in organ transplantation. In this review the principal news that occurred by 2013 are described. By, because some news refers to meeting, consensus conference or guidelines held in the late 2012 but published in 2013; others on the contrary were held in 2013, but published in the first months of 2014.

In these conclusions we highlight several points, which in our opinion represent new frontiers in transplantation. While the donor pool is not as large as it would be necessary, the donor shift towards the so called ECD realize new problems

in the organ allocations and in the organ preservation, Relevant news has been found in the field of antibody mediated rejection, both acute and chronic. This kind of rejection involves any solid organ, even if the majority of studies have been done in the kidneys. A new Banff conference has been held in 2013 and new classifications have been made whenever possible.

The ischemia reperfusion injury concerns also any organ. In this field the majority of researches have been made in liver transplantation. The innate immunity is involved and new drugs have been found or are on clinical trials. Pancreas transplantation is now a therapeutic option also for T2DM, even if a limiting factor is the shortage of pancreas available. Islet cell transplantation is improving with new techniques for implantation and for microencapsulation.

Heart transplantation has now optimal graft survival rate and also the MCS is evolving so to represent an alternative to transplantation in addition to bridge to transplantation. New strategies for primary graft dysfunction in lung transplantation have been found as well as a better understanding of the different types of chronic allograft dysfunction. New drugs appear at the horizon, principally for kidney transplantation. In particular, drugs targeting the B cells and the complement pathway are interesting, considering the relevance of ABMR. Other drugs for different organs such as liver, pancreatic islet and lung are being studied in clinical trials. Anti-inflammatory drugs enhance the effect of the immunosuppressant drugs.

The knowledge on tolerance is improving either applying bone marrow cells or mesenchymal stem cells. The infections and the cancers remain among the principal drawbacks in transplantation and several meetings and conferences have been held principally to elaborate guidelines to check and control HCV, HIV, CMV and others HHV.

The need to realize international registries for an improved knowledge of cancer epidemiology has been stressed by several authors. Finally a point of weakness in the field of transplantation is the differences that exist among the countries in the world. The different transplant rate depends also by the fact that in several countries peoples do not reach end stage disease. This probably represents the hardest frontier to be afforded.

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