

Health Council of the Netherlands

The benefit of HLA-matching in kidney transplantation





To the Minister of Health, Welfare and Sport
PO Box 20350
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Subject : presentation of advisory report
The benefit of HLA-matching in kidney transplantation
Your reference : IBE/E-2265501
Our reference : U 0543/MB/sl/631-H
Enclosure(s) : 1
Date : May 22, 2006

Dear minister,

I hereby submit for your attention a report on the benefit of tissue matching in kidney transplantation. The report has been compiled by a committee of the Health Council, taking account of expert input from the Council's Standing Committee on Medicine.

Over the last few decades, considerable advances have been made in the field of kidney transplantation. As a result, outcomes have improved greatly. Ever since the use of organs from deceased donors began in about 1970, the allocation of organs has been guided by HLA matching, i.e. matching based on the degree of compatibility between the donor's tissue type and the recipient's tissue type. In order to ensure the most suitable recipient for every organ that becomes available, the responsible organisations (in the Netherlands, the NTS and Eurotransplant) operate a policy of exchanging donor kidneys between centres and even between countries. The implementation of this policy is a logistically complex undertaking. Furthermore, despite international organ exchange, the complexity of the HLA system is such that only a minority of patients receive an organ that is a perfect match. Most transplant patients receive reasonably or moderately well-matched kidneys and consequently remain permanently dependent on anti-rejection medication, which is not free of side effects.

However, in the Netherlands and elsewhere, the recent introduction of powerful new immunosuppressant drugs has brought the need for continued HLA matching into question. It has also been suggested that the long-distance exchange and cooled transportation of donor kidneys leads to unnecessary degradation of the organs due to 'cold ischemia' – the temporary interruption of a flow of oxygen-rich blood through the organ. Moreover, there has been speculation that there may be no difference in outcome between transplants

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Page : 2
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involving well-matched donor kidneys and those involving moderately well-matched organs, provided that the cold ischemia time is kept short and that sufficiently powerful anti-rejection medication is administered. If the latter hypothesis were to prove valid, a comprehensive review of the donor organ allocation policy would be required.

The Health Council committee that considered the questions set out above performed a thorough analysis both of the scientific and practical aspects of HLA matching, and of the implications of prolonged, high-dosage anti-rejection therapy. The committee waited for the findings of research then in progress to become available, in order to take them into account; that is why it has taken until 2006 to complete this report. On the basis of the most recent data, the committee came to the ultimate conclusion that good tissue matching remains an important precondition for the achievement of positive long-term transplant outcomes. It is accordingly recommended that the allocation policy for donor kidneys should continue to be based upon HLA matching, as a key, objective criterion. Nevertheless, the committee makes the additional point that the criteria for tissue matching could be simplified, thus increasing the transplant opportunities for patients – in particular those who have to wait a long time because of the difficulty of finding a well-matched organ. Such a move could have the added benefit of easing the logistic challenges of matching and exchanging kidneys.

I endorse the conclusions and recommendations of the committee that prepared the report and I advise you to take the report's content into account in the further development of national and international allocation policy for donor organs.

Yours sincerely,

(signed)

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The benefit of HLA-matching in kidney transplantation

to:

the Minister of Health, Welfare and Sport

No. 2006/08E, The Hague, May 22, 2006

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The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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Preferred citation:

Health Council of the Netherlands. The benefit of HLA-matching in kidney transplantation. The Hague: Health Council of the Netherlands, 2006; publication no. 2006/08E.

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ISBN: 978-90-5549-888-8

Contents

Executive summary *11*

- 1 Introduction *13*
 - 1.1 Immunity, tissue matching and transplantation *14*
 - 1.2 The role of tissue matching *14*
 - 1.3 The problem of long waiting periods *15*
 - 1.4 Allocation policy *15*
 - 1.5 Critical questions *16*
 - 1.6 Request for advice *16*
 - 1.7 Structure of this report *17*
-
- 2 The effect of HLA matching *19*
 - 2.1 Tissue matching and rejection *19*
 - 2.2 Tissue typing *20*
 - 2.3 HLA match and transplant survival *21*
 - 2.4 HLA matching in Eurotransplant *25*
 - 2.5 The success of unrelated living donor transplants *29*
-
- 3 The effect of HLA matching and the influence of immunosuppression *33*
 - 3.1 Does modern immunosuppression make HLA matching unnecessary? *33*
 - 3.2 HLA matching and maintenance immunosuppression *35*
-

3.3	The likelihood of malignancy after transplantation	35
3.4	Conclusion	36
<hr/>		
4	Possible correlation between HLA matching and cold ischemia time	37
4.1	How may the problem be analysed?	37
4.2	Conclusions	41
<hr/>		
5	For which patients is HLA matching essential?	43
5.1	Perfectly matched patients	44
5.2	Highly immunised patients	44
5.3	Patients with rare HLA phenotypes	46
5.4	Patients who are recommended for priority exchange, but not on the basis of HLA compatibility	46
5.5	Conclusion	47
<hr/>		
6	Strategies for improving kidney transplant survival	49
6.1	Enlarging the donor pool	49
6.2	Prognostic transplant survival index	50
6.3	Matchability concept	50
6.4	Better prognoses for re-transplants	51
6.5	Cross-reactive antigen group matching	52
6.6	Differential immunogenicity of HLA mismatches: HLAMatchmaker	53
6.7	Matching at the HLA-DR-level only	53
6.8	Conclusion	54
<hr/>		
7	Non-immunological considerations	55
7.1	Cost	55
7.2	Objective medical criterion	57
<hr/>		
8	Conclusions and recommendations	59
<hr/>		
	Annex	59
A	References	61
B	Request for advice	71
C	The Committee	73

Executive summary

A successful kidney transplant is the most effective treatment for patients with end-stage renal insufficiency, and provides the best chance of good long term rehabilitation while restoring the quality of life of the patient. When undertaking these procedures the transplant physician will aim for the best possible degree of tissue compatibility between the donor and the recipient. This has always been the ground rule in the allocation of cadaveric donor organs. However, a perfect tissue match (fully identical HLA-A+B+DR antigens, or a zero HLA-mismatch) can be achieved only for a minority of the patients. In particular those patients who have become highly immunized (usually because of a previous transplant), or patients with a rare HLA-phenotype, are difficult to match and therefore seem condemned to excessively long periods on the waiting list. Mainly because of the very success of kidney transplantation, the number of patients on the waiting list has grown tremendously during the past decades, and this has resulted in a corresponding increase of the mean waiting time. In order to continue to achieve good outcomes and acceptable waiting times for the majority of patients, it is crucial to have access to an (international) pool of patients and donors, and to exchange available donor organs. This notion laid the foundation for Eurotransplant and other similar organ sharing organizations.

The arrival of new and potent immunosuppressive drugs has significantly improved the outcome of transplantation, in particular by reducing the incidence and seriousness of rejection episodes. This however, has also fuelled the notion that modern immunosuppressive regimens may in fact be capable of eliminating

the beneficial effect of HLA-matching and have made redundant the effort to achieve good histocompatibility. This would mean that aiming for the best possible HLA match is no longer taken into account when allocating donor organs, and also that international sharing of organs, with its complex logistics and extended cold ischaemia times (i.e. the interval between retrieval and implantation of the organ) could be omitted.

Careful analysis of kidney transplant outcomes, made available by international databases (such as the Eurotransplant Database, the CTS Registry and the UNOS Database) has learned however, that the effect of HLA-matching is still significantly present, despite more effective immunosuppression, shorter cold ischaemia times and improved logistics. A beneficial HLA-match will generally result in a significantly improved outcome, in particular good long term graft survival. The use of high-dose and potent immunosuppressive maintenance therapy, however, does increase the long term risk of adverse effects, such as malignancy. Putting an end to the international exchange of organs, and giving up the pursuit for a compatible HLA-match, on the other hand, would seriously jeopardize the chance to find compatible grafts for difficult-to-match patients. These facts speak in favour of continuing an allocation policy based on HLA-matching. Nevertheless it seems actually possible to further simplify and optimize allocation rules for donor kidneys, as well as relevant match-criteria (as has been already undertaken in the new ETKAS-model introduced by Eurotransplant).

Recent studies also point to a new approach, in which donor and recipient matching is focused primarily on good HLA-DR compatibility, and compatibility for class I antigens (HLA-A and -B) is considered only as an additional matching criteria. This may lead to further simplification of allocation criteria, without any loss of quality of the transplant outcome. Another important objective is to achieve acceptable results and waiting times in particular for the category of difficult-to-match patients. This effort has resulted, among others, in the 'Acceptable Mismatch' Programme recently implemented by Eurotransplant. Such developments result in a more just allocation and stimulate the efficient use of the severely limited supply of donor organs, which still presents the main obstacle in organ transplantation today.

Introduction

Kidney transplantation is the preferred treatment for patients with a terminal renal insufficiency. Amongst such patients, both the short-term and the long-term survival rates associated with transplantation are better than those associated with dialysis (Wol99). Moreover, further significant improvements in transplant outcomes have been secured in the last decade, building on the success previously achieved following arrival of the anti-rejection drug ciclosporine. The recent advances are attributable to the introduction of new anti-rejection medications, such as mycophenolate mofetil (MMF-Cellcept®) and tacrolimus (FK506-Prograf®), which have reduced both the incidence and the seriousness of acute rejection episodes following transplantation. The improved post-transplantation prognosis has contributed to sharp growth in the demand for donor kidneys. However, there has been a persistent structural shortfall in the corresponding supply. The shortage of cadaver donor organs (organs from deceased donors) makes it very important that available organs are allocated to the many waiting patients using strict and carefully formulated criteria designed to optimise the prospects of survival. Driven partly by the length of both the transplant waiting list (national total on 31 December 2004: 1,130 people) and the waiting period (2004 average: 1,493 days), we have witnessed substantial growth in the number of kidney transplants involving living related or unrelated donors in the Netherlands (250 out of a total of 673 kidney transplants in 2004). However, this report is confined to the allocation policy for cadaver donor kidneys and the role of HLA matching within that policy.

1.1 Immunity, tissue matching and transplantation

The significance for transplantation of the primary mechanisms of immunity and rejection was first established by experiments involving skin transplantation and tumour modelling in animals. As long ago as 1901, Landsteiner defined the ABO blood group system and described its significance for blood transfusion practice (Lan01). Shawan went on to observe in about 1919 that blood group compatibility was also an important factor in the survival of skin transplants (Sha19). Subsequent researchers (particularly Murphy, Gorer and Landsteiner once more) laid the basis for development of a genetic transplantation theory and for Snell's discovery of the system of tissue compatibility (histocompatibility) in mice in 1948 (Gor36, Lan31, Mur18, Sne48). However, the precise nature and significance of human transplant rejection was not properly understood until Medawar and Gibson (1943-44) published the results of experiments involving the transplantation of skin between rabbits, showing that rejection is a form of acquired immune response to foreign tissue antigens (coded by a cluster of genes in the major histocompatibility complex (MHC)) (Gib43, Med44, Med46).

In the 1950s, Dausset, van Rood and Payne finally (and independently from one another) established which of the recipient's antibodies react to the donor's white blood cells (leukocytes) (Dau54, Pay58, Roo58). The discovery of these leukocyte antigens laid the basis for the tissue typing now conventional in transplantation and enabled the hereditary basis of these antigens to be established (Pay61, Roo59).

1.2 The role of tissue matching

The outcomes of kidney transplantation are influenced by numerous factors, including in particular the tissue match between the donor and the recipient (the HLA – human leukocyte antigen – compatibility) (Cec98). It was apparent from research carried out in the early years of kidney transplantation that the matching of donor and recipient on the grounds of tissue compatibility (tissue matching), involving selection to minimise the number of antigen mismatches between the donor organ and the patient, has a positive influence on the transplant's short-term and long-term survival prospects (Gje89). In consequence, HLA matching has become the universal basis for allocating scarce donor organs to waiting patients as fairly as possible. A matching-based allocation strategy implies giving each available donor kidney to the best-matched recipient, even if he or she is in another part of the country or even in another country. Such

international organ sharing is the primary reason for the existence of organisations such as Eurotransplant (founded in 1967), which allocates organs in a region that embraces the entire Benelux, Germany, Austria and Slovenia (a population of roughly 120 million) (Roo67).

1.3 The problem of long waiting periods

In the recurring parliamentary debates regarding the problems surrounding organ donation (particularly the long waiting list and the reluctance to donate) and the evaluation of the Organ Donation Act (WOD), repeated reference has been made in recent years to the donor organ allocation system and to the criteria used in that context. The WOD states that allocation must be exclusively on the basis of medical criteria, such as the donor's and recipient's blood and tissue compatibility, the medical urgency of the recipient's condition and other matters associated with the condition of the organ, or, if those factors are not decisive, with the length of time that the recipient has been waiting (WOD, Section 18, subsection 3).

These explicit criteria are intended to ensure fair and transparent distribution of the scarce donor organs that become available. The aim is also that an appropriate organ should be found for every patient within a reasonable space of time. The appropriateness of an organ depends to a significant extent on the patient's tissue characteristics, age, immunisation status (the presence of antibodies to the donor) and the medical urgency of his/her condition. It is unrealistic to expect to find a donor with a perfect tissue match (all six HLAs matching) for every patient. However, it is not the case that an imperfect match necessarily leads to an unfavourable outcome (particularly prolonged transplant survival).

1.4 Allocation policy

The existing donor organ allocation policy of the Dutch Transplantation Foundation (NTS) is based on and follows the system that is used internationally by the Eurotransplant organisation. ETKAS (the Eurotransplant Kidney Allocation System) was introduced in 1996 and is based on the premise that optimal transplant outcomes depend on ensuring the best possible tissue typing and matching (HLA compatibility), because that minimises the short-term and long-term risk of the transplant being rejected. The donor kidneys that become available are shared amongst transplantation centres, and amongst countries, in order that every organ can be allocated to the most suitable possible recipient.

Thus, the entire patient population of the Eurotransplant region forms the pool from which suitable recipients may be selected, on the basis of the criteria referred to above. This implies that the organisational and logistic arrangements have to be geared to the possibility that donor organs need to be transported over considerable distances. ETKAS's mandatory exchange rules prioritise allocation to patients who have a perfect tissue match with the donor (6-antigen match, zero mismatch), to patients who are highly immunised or difficult to match because of their tissue characteristics, and to children. Under ETKAS, there is also a special allocation programme for older patients (Eurotransplant Senior Program), in the context of which the tissue match is disregarded and transplants are performed after the shortest possible cold ischemia time.

1.5 Critical questions

In recent years, the allocation system described above has been the subject of frequent debate, both in scientific circles (Asw93, Gil02, Koe02) and amongst public health policy makers (Dor02). So, for example, at a General Meeting between the Parliamentary Standing Committee on Public Health and the then Minister of Health, Welfare and Sport, in February 2002, the following critical questions were raised (TK02):

- Has the introduction of new, more powerful anti-rejection medication made HLA matching less important or even superfluous?
- Is it not the case that the exchange of donor organs leads to the organs being in transit for extended periods, which is detrimental to their quality, due to cold ischemic injury?
- Would it be better to allocate donor organs on a local or regional basis, rather than internationally, and to disregard HLA compatibility, relying instead on powerful immunosuppressant therapy?

1.6 Request for advice

Towards the end of 2002, prompted in part by the meeting with the Standing Committee, the Minister of Health, Welfare and Sport asked the President of the Health Council to report on the present-day importance of HLA matching and, in particular, to address the questions and issues referred to above (see Annex 1). The Minister also asked that the Health Council should consider whether the findings of its analysis had implications for the existing allocation system, so that appropriate amendments to the WOD could be considered.

1.7 Structure of this report

Broadly speaking, the structure of this report follows the critical questions raised in the public parliamentary debate, which the Minister of Health, Welfare and Sport reiterated in his request for advice.

Section 1 forms an introduction to the problem of tissue typing in kidney transplantation and sets out the reservations that some commentators have expressed regarding the existing organ allocation policy. In Section 2, consideration is given to the effect of HLA matching on kidney transplantation outcomes and the main mechanisms and concepts relevant to tissue typing and rejection. Section 3 deals with the development and use of modern immunosuppressant therapy and its implications for HLA matching. The possible cancer risk associated with the prolonged use of such medication is also described. In Section 4, the Committee considers whether HLA matching has adverse implications for the duration of cold ischemia and thus for the quality of the transplanted organs. Sections 5 and 6 identify the categories of patient for whom HLA matching is essential to the success of their kidney transplants, and presents a number of recommendations for the further enhancement and simplification of the organ matching and allocation system. Finally, in Section 7, the Committee looks at a number of spin-off effects of HLA matching, such as cost savings in the care system. Section 8 contains a résumé of the main conclusions and recommendations.

The effect of HLA matching

The human immune system does not respond to the body's own structures, but does respond to foreign materials, be they pathogenic viruses or bacteria, or transplants introduced with benign intent. In a transplanted organ or tissue, the immune system distinguishes the red blood groups in the ABO system and the complex tissue groups that belong to the HLA system (Kle00). The latter tissue groups were first identified on white blood cells (leukocytes) and are therefore known as human leukocyte antigens (HLAs) (Dau54, Roo58). If there is a significant difference between the donor's HLAs and the recipient's HLAs, there will be a violent immunological response (rejection). If on the other hand the tissues are similar (histocompatible), the response will be much milder. If all tissue groups are the same, such as in the case of transplantation between identical twins, there should be no rejection at all. This is indicative of the significance of hereditary factors in the rejection process.

In the transplantation of organs and tissues, testing to determine the degree of histocompatibility between the donor and recipient is a vital process, which helps to determine the outcome of the intervention.

2.1 Tissue matching and rejection

The complexity of the HLA system (particularly its polymorphic character: there are more than 20 billion possible tissue combinations) makes it unrealistic to seek a perfect tissue match for every patient. Perfect matches are especially

improbable if organs are sourced from unrelated, deceased donors. In present-day transplantation practice, one must therefore expect that many recipients will develop a rejection response to the foreign HLAs on the donor organ. The foreign HLA molecules on the transplant are identified by the recipient's T cells and B cells. The T cells are responsible for the cellular rejection response. There are two types of T cell: 1) cytotoxic T cells, which can destroy organs by direct cell-to-cell contact, and 2) helper T cells, which play a regulatory role by producing signal substances (cytokines). The B cells produce mainly antibodies, which are capable of causing organ damage (humoral response).

Rejection is normally controlled using immunosuppressant (i.e. rejection-suppressing) drugs, which patients have to take after receiving the transplant – usually for the rest of their lives. It is largely the availability of immunosuppressant drugs that has enabled sizeable clinical transplant programmes, in which most of the organs come from incompatible donors. These drugs also make a very significant contribution to positive transplantation outcomes (transplant function and survival). In the last few years, a series of new immunosuppressant drugs has been developed, which have further reduced rejection problems.

2.2 Tissue typing

The HLAs (which determine the tissue type) are localised on the short arm of chromosome 6, and are genetically determined: a child inherits half its HLAs from its mother and the other half from its father. Distinction is made between the HLA molecules of the MHC (major histocompatibility complex) class I, subdivided into HLA-A, -B, and -C) and class II, subdivided into HLA-DR, -DQ, and -DP. In the context of organ transplantation, the class I antigens known as HLA-A and HLA-B, and the class II antigen HLA-DR are considered to be particularly influential. The class I antigens are found on the surfaces of practically all nucleated cells and on blood platelets. HLA-DR molecules of MHC class II are expressed on antigen-presenting cells, such as dendritic cells. These various HLA molecules have numerous variants (alleles), each of which is identified with a number.

A patient's or donor's HLA type is normally given as a combination of two A antigens, two B antigens and two DR antigens. One of each pair of antigens is inherited from the person's father, and the other from the person's mother. Therefore identical twins have identical HLAs, and a parent and child have half their antigens in common (they are 'haploidentical'). Finally, siblings will normally be 25 per cent identical.

If the donor and the recipient are not blood relations, the situation is more complicated. Although not impossible, a perfect tissue match (6 identical HLAs) is highly unlikely, because of the polymorphy of the HLA system. However, for a successful transplant, a partial tissue match with the donor (e.g. two HLA-DRs and one HLA-A and -B in common) is usually sufficient. The chances of finding such a partial match are a lot greater if the pool of donors and recipients is bigger (as in the Eurotransplant region).

In the past, tissue typing was performed serologically (with sera from pregnant women), but this method was not entirely reliable (Myt90, Ope91a). Nowadays, molecular-biological techniques are preferred. Such DNA typing is more accurate and the DNA can be isolated from various types of body cell and even from old blood, which isn't suitable for serological typing. The introduction of DNA typing has also led to the identification of more HLA molecule variants. In theory, discovery of the new variants makes HLA matching more complex than ever, but in practice it seems that the DNA-level differences between HLA molecules have little clinical relevance in terms of the likelihood of rejection.

2.3 HLA match and transplant survival

This report examines only the influence of the HLA match on the transplant outcome; it does not explore the significance of other immunological barriers, such as ABO blood group incompatibility or crossmatch positivity (the presence of antibodies to the donor). In the context of organ transplantation, it is recognised that the blood group barrier must be respected, otherwise acute rejection of the transplant will follow. Every individual naturally has circulating antibodies against incompatible blood groups (e.g. A against B). Strict ABO compatibility between recipient and donor is therefore a feature of conventional transplantation procedures. A similar approach is taken with HLA antibody positivity: approximately 20 to 30 per cent of patients have anti-HLA antibodies that can preclude transplantation. In the future, however, it may be possible to overcome these barriers. Trials have recently been carried out, involving the use of plasmapheresis and immunosuppressant medication to prepare a recipient for the implantation of a transplant from an ABO-incompatible donor (Tyd03, Tyd05). The use of desensitisation by means of intravenous human immunoglobulin therapy (IVIG) has recently been introduced for the treatment of positive-crossmatch patients. However, this approach can only be used for living donor transplantation procedures (Jor03a, Jor03b).

Transplantation follow-up studies

For the last thirty-five years, HLA matching has been the norm for kidney, cornea and bone marrow transplants at most centres. The outcomes of these procedures have also been monitored and recorded (Cec00, Ope99a, Smi96, Tak00). Consequently, data are now available for several hundred thousand transplants (from, for example, the Eurotransplant Registry, the US UNOS Database and the Collaborative Transplant Study (CTS) Database). Using these data, the effect of HLA matching on the outcomes of transplantation can be retrospectively analysed.

As long ago as 1985, Van Rood et al demonstrated that HLA matching (then involving only MHC class I antigens) had a significant influence on long-term kidney transplant survival. This conclusion was based on data on the first 124 patients who received kidneys between 1967 and 1972 and concerning whom data were recorded by Eurotransplant. The analysis looked at the survival of such patients after a period of more than ten years (Hoo85). Roughly fourteen years after transplantation, half of the donor kidneys given to identically matched patients (patients with zero HLA-A and -B mismatches) were still functioning, while 10 per cent of these patients had experienced chronic rejection. Amongst patients who received poorly matched (incompatible) donor organs, the transplant survival was only 22 per cent, and more than half had experienced chronic rejection.

From the latter findings and the results of numerous follow-up studies, it is apparent that transplant survival is most likely in recipients who exhibit a perfect (6-antigen) tissue match. The chance of survival is smallest in patients who exhibit a complete (6-antigen) mismatch. Between those two extremes, the rates of the transplant survival diminish incrementally with decreasing tissue compatibility (see also Figure 1). The data also show that HLA-DR compatibility is most important in the first period after transplantation (less rejection), while HLA-B and, to a lesser extent, HLA-A compatibility mainly influence longer-term transplant survival. (Tho90, Zan96). In light of those observations, most centres have since the mid-1980s included MHC class II antigens (HLA-DR) in their HLA typing and allocated organs to recipients who exhibit a perfect match or a HLA-A+B+DR match, or sometimes only an HLA-B+DR match.

Analysis results

The most complete and robust data on the influence of HLA matching on kidney transplant survival are presented in the publications by Opelz, who brought

together data on more than 100,000 transplants at more than 300 centres in 45 countries in the Collaborative Transplant Study (CTS) (Ope99b, Ope05). In his most recent analysis (covering the period 1995-2004), Opelz showed that there is a clear correlation between the degree of HLA-A+B+DR matching and transplant survival: the greater the number of mismatches (between zero and six), the poorer the prospects for survival. When such large numbers of patients are studied, the differences between the curves are highly significant (see Figure 1).

The differences between transplants involving a perfect match (0 MM), a favourable match (1-4 MM) and an unfavourable match (5-6 MM) can be illuminated by extrapolation from the outcome data to obtain transplant survival rates after twenty years and transplant half-lives (the transplant half-life being the time after which 50 per cent of the donor kidneys are still functional).

Opelz does observe that the disparity between the zero-MM and 6-MM curves has steadily diminished in the last twenty years (from more than 15 per cent to 10 per cent difference in transplant survival). This may be attributable to the introduction of more effective immunosuppressant drugs. Nevertheless, the influence of HLA matching currently remains significant.

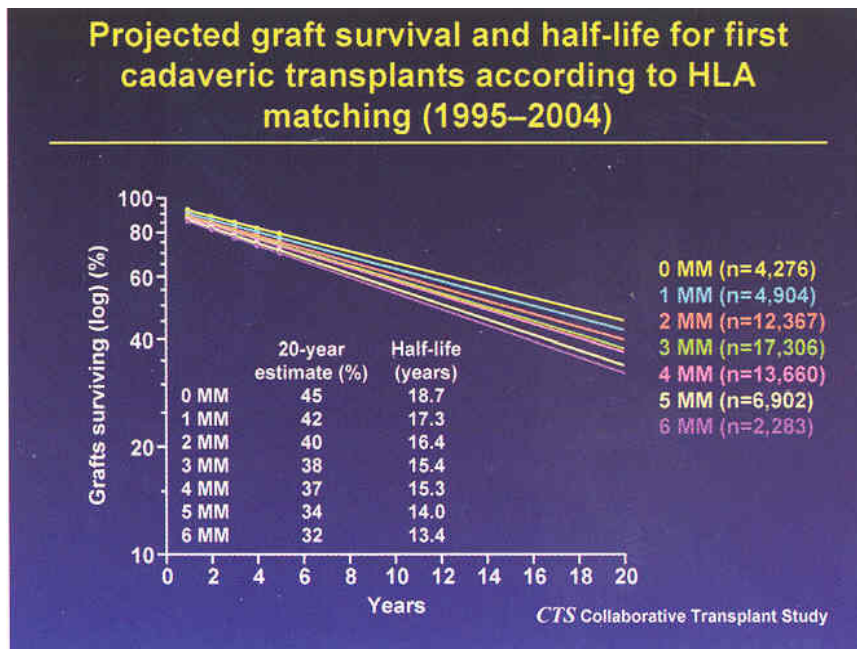


Figure 1 Transplant survival and kidney transplant half-life for various degrees of HLA compatibility. Source: Opelz 2005.

Similar outcomes were reported by Morris et al, who performed an analysis of kidney transplant survival in 6,363 cases of initial transplantation with a cadaver donor, performed between 1986 and 1993, at 23 centres in the UK (Mor99). The team found that the degree of HLA matching had a significant influence on transplant survival after five years. As one would expect, the best outcomes were obtained in patients who exhibited no HLA-A+B+DR mismatches (zero MM). Next came the group who exhibited one mismatch at the A or B locus (1 MM) or one mismatch at both the A and B loci, but no DR mismatches (2 MM). The poorest results were found in the group with one or two DR mismatches, plus one or more mismatches at the A and B loci. Transplant survival in the three groups after five years was, respectively, 74, 67 and 60 per cent.

On the basis of this analysis, Morris et al concluded that HLA matching was always important for the attainment of optimum transplant outcomes. They accordingly recommended that whenever a zero-MM recipient was available for a donor kidney on the national waiting list, that patient should be prioritised (mandatory exchange). In cases where there was a 'favourable match' (1 or 2 MM, but no DR mismatch), one of the donor's kidneys should preferably be allocated to the national waiting list, while the other could be utilised by the regional centre.

In 2000, Takemoto et al published an analysis of the results of twelve years of US experience with the national allocation of kidneys, on the basis of HLA matching (Tak00). Since 1987, the US United Network for Organ Sharing (UNOS) has operated a national exchange programme for donor kidneys (UNO95). In the context of that programme, nearly 89,000 transplants were performed between 1987 and 1999. In those cases, a total of 7614 kidneys were allocated through the national pool on the basis of an identical HLA match (zero HLA-A+B+DR mismatches); that figure represents approximately 8.5 per cent of all kidney transplants. Outcomes in this group were compared with those in a large group of patients with one HLA mismatch, to whom kidneys were not allocated through the national programme. After correction for demographic differences and mortality, the difference in transplant survival between the two groups was more than 10 per cent, with a half-life of 12.5 years for the zero-mismatch group and 8.6 years for the one-mismatch group. Notably, exchange in the context of the national programme was not associated with an increased cold ischemia time; the average was 22 hours for both groups.

Takemoto et al accordingly concluded that allocation on the national scale, on the basis of HLA matching, was associated with improved transplant survival and a lower incidence of rejection. The team estimated that, if the programme

were discontinued, 0-MM transplants would decline to a mere 2 per cent of the total.

2.4 HLA matching in Eurotransplant

Within the Eurotransplant programme, donor kidney allocation used to be based primarily on the best possible HLA match (HLA-A+B+DR) between donor and recipient, since it was assumed that this must lead to the most favourable outcome (transplant survival) for the patient (Mee98, Per77, Per78, Per85, Per02). However, this policy had the unintended side effect of leading to an increase in the number of patients – particularly highly immunised patients – who remained on the waiting list for a prolonged period. Consequently, the policy was changed.

ETKAS allocation algorithm

In 1996, Eurotransplant introduced a new allocation model for donor kidney allocation: the Eurotransplant Kidney Allocation System (ETKAS). Under this system, all donor kidneys that become available from deceased donors are transferred to the central pool for allocation to waiting patients on the basis of a points system. Points are awarded for the degree of HLA matching, the length of time a prospective recipient has been waiting, the mismatch probability (see Section 6), the distance to the transplantation centre and the import-export balance between the Eurotransplant member countries. With regard to the degree of HLA matching, allocations entail zero- or one-HLA-DR mismatches wherever possible. This is achieved in more than 90 per cent of cases, so that 2-HLA-DR mismatch transplants are almost always avoided (Per01, Per02).

The objectives of this new allocation model were as follows:

- Reduced average and maximum waiting periods for renal patients
- Better transplant prospects for patients with rare HLA phenotypes and for homozygotic patients (i.e. patients with an identical HLA at one or more HLA loci)
- A reasonable exchange balance between member countries
- Good HLA compatibility for as many patients as possible and therefore optimum transplant survival.

Results

Between March 1996 and March 2005, a total of 28 167 transplants were performed in the Eurotransplant region as a whole using kidneys allocated under the new system (Smi02). In this period, the percentage breakdown of the transplants according to the number of HLA-A, -B and -DR mismatches was as follows:

Table 1 Breakdown of Eurotransplant transplants according to HLA-A+B+DR mismatches, 1996-2005.

Number of mismatches	Percentage of transplants
0	21.4
1	8.4
2	27.0
3	30.6
4	10.3
5	2.1
6	< 1
Total	100

Broken down according to the number of HLA-DR mismatches only, the figures are as follows:

Table 2 Breakdown of Eurotransplant transplants according to HLA-DR mismatches, 1996-2005.

Number of HLA-DR mismatches	Percentage of transplants
0	41
1	50
2	9

As the data presented above show, the move away from strict HLA matching under the new system has not led to a decline in the number of transplants involving a perfect (zero-MM) match: such transplants have continued to account for > 20 per cent of the total. The number of transplants involving unfavourable matches (5 or 6 MM) has also remained low, at < 4 per cent. Furthermore, the introduction of ETKAS has resulted in significantly more long-wait patients (> 5 year on the waiting list) receiving transplants: 21 per cent, compared with 10 per cent under the old system. Similarly, the number of highly-immunised patients for whom a suitable donor has been found (under the Acceptable Mismatch Programme) has risen. Finally, the average waiting period

for children (up to 16 years old) has fallen, due to the number of transplants rising by more than 17 per cent (Per02).

Three-year transplant survival in patients allocated kidneys through ETKAS has been good: the average survival rate for the whole group is 78 per cent. Across the entire recipient population, HLA matching can be seen to have a significant influence: transplant survival is 83 per cent in the group with zero-HLA-A+B+DR mismatches, compared with 71 per cent in the group with 5 or 6 mismatches (see Figure 2).

HLA matching and rejection

The occurrence of rejection responses in the first period after transplantation is a key determinant of transplant longevity and the rate of longer-term transplant loss. The number of rejection episodes in the first year is therefore a predictor of donor kidney longevity and later chronic transplant rejection. The development of modern anti-rejection drugs has had a major impact in this area: acute rejection in particular can now be effectively controlled and the incidence of such rejection has consequently fallen from 30 per cent to 15 per cent. This in turn has led to substantially improved transplant survival.

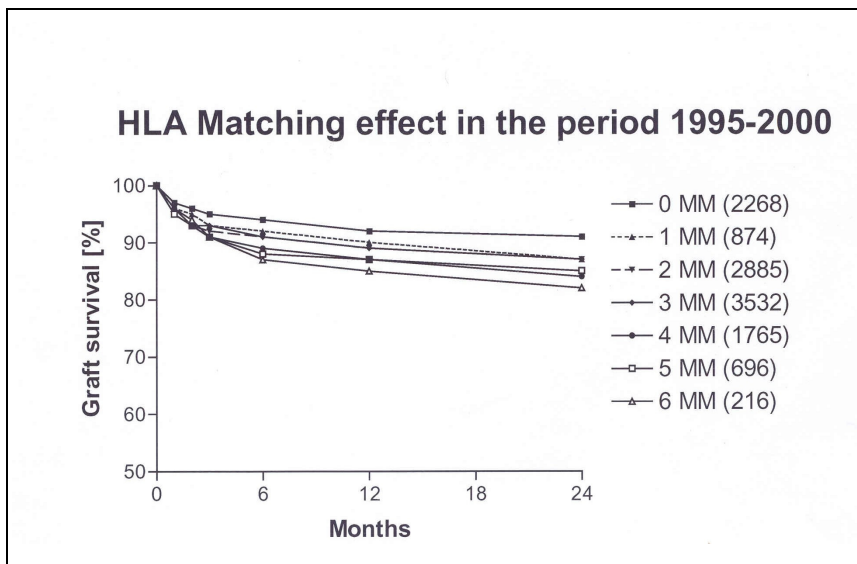


Figure 2 Transplant survival and degree of matching in Eurotransplant 1995-2000.

Research has demonstrated that the incidence of acute rejection correlates to the degree of HLA compatibility between donor kidney and recipient (Dox04). In a retrospective analysis of data on kidney transplant patients (from the CTS Database) in the period 1995-2004, Opelz et al found, for example, that there was a strong correlation between the degree of tissue match and the number of rejection episodes treated in the first year after transplantation (Ope05). This is illustrated in Figure 3.

In a group of nearly 20,000 first-time recipients of kidneys transplanted from cadaver donors, only 12 per cent of patients with no HLA mismatches required treatment to suppress rejection. The percentage requiring such treatment rose incrementally with increasing tissue mismatch: in the group with 5 and 6 mismatches, rejection responses required treatment in approximately 22 per cent of cases. The influence of tissue matching on rejection phenomena continues after that initial period; in later years the differences described above persist and there is a significant correlation between the number of HLA mismatches and the number of treated rejection episodes (although the incidence of rejection in later years is generally lower, at 3 to 5 per cent). This may explain the better longer-term survival in patients with good HLA matches (Ope05).

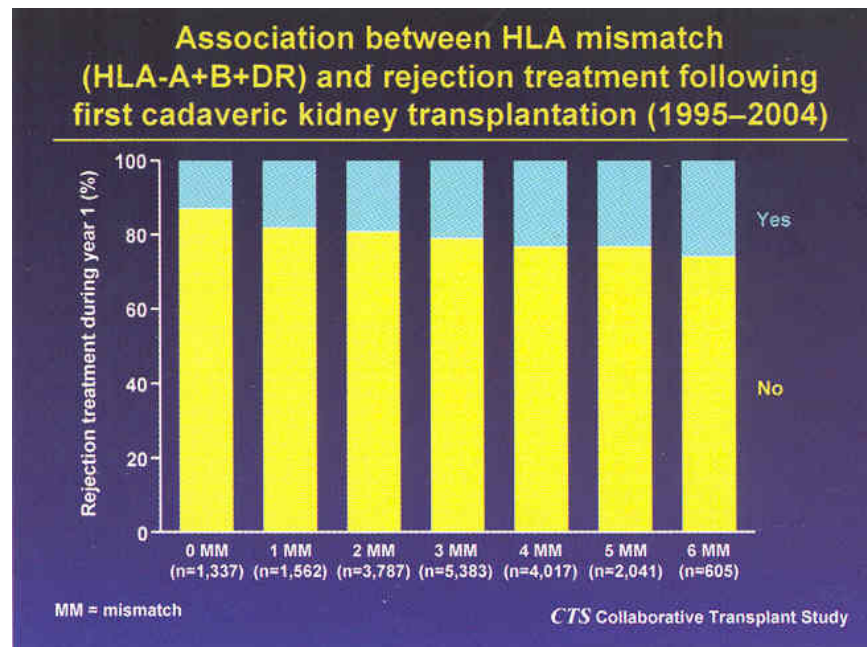


Figure 3 Correlation between HLA match and incidence of rejection episodes. Source: Opelz 2005.

Acute rejection immediately after transplantation is usually detected on the basis of elevated serum creatinine and confirmed by biopsy. However, it has recently become clear that, even when the transplant appears to be functioning well, gradual rejection can occur, potentially resulting in chronic nephropathy and transplant loss. This is referred to as subclinical acute rejection (SAR); it can be detected even in the first three months after transplantation by means of biopsy (Mor06, Nan03). Research into the determinants of SAR has very recently shown that HLA compatibility with the donor is one of the risk factors. The number of HLA-DR mismatches in particular appears to be closely related to the development of SAR in the period shortly after transplantation. On the basis of this observation, it is possible to investigate suitable forms of prevention or treatment (Nae06). The influence of HLA-DR matching on the incidence of SAR again demonstrates that, even with the availability of powerful anti-rejection medication, HLA matching remains extremely important in the context of kidney transplantation.

2.5 The success of unrelated living donor transplants

In 1995, Terasaki et al published the results of research into transplant survival in patients who had received a kidney from a living donor, which involved comparison with the survival of cadaver donor kidneys (Ter95). Amongst some nephrologists, the findings of this study cast further doubt on the significance and practical value of HLA matching in kidney transplantation (Jua98, Naj95). Terasaki's team performed a retrospective analysis of the outcomes of approximately 50,000 kidney transplants (as recorded in the UNOS database); these outcomes were then compared with those associated with related and unrelated living donors. Most of the blood-related donors were parents and siblings. The unrelated donors were mainly spouses and partners, but also included some friends and colleagues. Notably (and unexpectedly), the survival of organs transplanted from genetically unrelated donors was almost exactly the same as that of organs from related donors (with a single haplotype match). Moreover, the outcomes with unrelated living donors were in all cases better than those associated with deceased donor transplantation. These findings are illustrated in Figure 4.

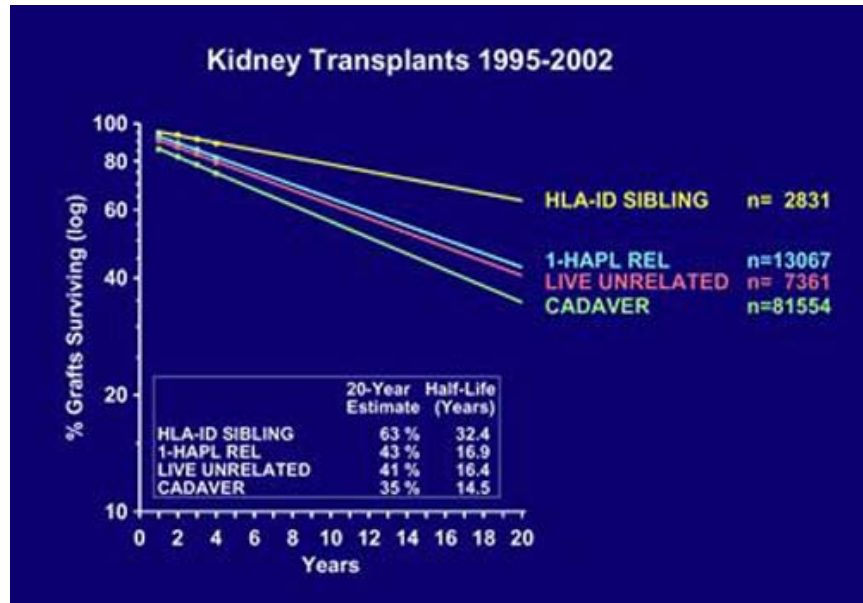


Figure 4 Survival of kidneys transplanted from related and unrelated living donors, compared with survival of kidneys transplanted from cadaver donors. Source: Opelz 2003.

In living donor transplantation, the main focus is normally on the blood group match and the absence of antibodies to the donor, rather than on HLA compatibility. Consequently, it has been suggested that the findings described above indicate that HLA compatibility and *a priori* matching is less important in kidney transplantation than has generally been assumed. It is indeed the case that most unrelated living donor transplants involve moderate or complete tissue mismatches (4-6 mismatches), yet result in transplant survival rates that are almost the same as those associated with related donor-recipient combinations (and a single haplotype match): the five-year transplant survival was 76 per cent with related combinations and 75 per cent with unrelated combinations. That equates to a half-life of 16.9 years for the related combinations and 16.4 years for the unrelated combinations (see also Figure 4).

It is therefore pertinent to ask whether the HLA match has no significance in unrelated donor-recipient combinations, and whether HLA compatibility also plays a less important role in kidney transplantations with a deceased donor.

Opelz analysed the outcomes of kidney transplants with unrelated living donors, using data from the CTS database, and found a weak association between the HLA match and the rate of transplant survival (Ope98, Ope03). However,

because very few unrelated donor-recipient combinations involve a high degree of HLA compatibility (as one would expect with genetically unrelated donors and recipients who are not selected by matching), the observed association is not statistically significant.

In search of an explanation for the findings described above, Opelz highlighted a number of interesting points to come out of his analyses:

- 1 A considerable difference in transplant survival rates exists between living-donor transplants involving perfectly tissue-matched donor-recipient combinations (identical twins), and haploidentical combinations (parent-child combinations and sibling combinations). The discrepancy in the ten-year transplant survival rates of these two groups is about 10 per cent, which corresponds to half-lives of 32 years and 17 years, respectively. It is reasonable to believe that these differences are attributable to the difference in the closeness of the HLA match (identical versus haploidentical tissue types).
- 2 There is a similar difference in transplant survival rates between living-donor transplants involving HLA-identical donor-recipient combinations, and transplants involving perfectly tissue-matched cadaver donors (6-antigen match). The discrepancy between the three-year survival rates is 9 per cent, in favour of the HLA-identical twins. The incidence of rejection in the first year after transplantation is also significantly lower in the latter group. These differences cannot be attributed to any difference in HLA compatibility.

Opelz suggests that the explanation for the differences described above is likely to be the difference in quality between kidneys from living donors and those from deceased donors. Living donors are usually younger (20 to 40 years old) and in good health (strict selection criteria). Furthermore, the organs are usually implanted more quickly after excision (short cold ischemia time), and have not suffered the harmful effects of brain death. Opelz reported that this hypothesis was supported by an analysis, in which transplant survival following procedures involving HLA-identical twins was compared with survival following procedures involving zero-mismatch cadaver donor-recipient combinations and all donors were aged between twenty and forty. This analysis found very little difference between the two groups in terms of transplant survival rates.

The analyses described above support the conclusion that the good outcomes of unrelated living donor transplants should not be interpreted as indicating that the matching of recipients and donors on the basis of HLA compatibility is not generally as important as previously supposed. The favourable outcomes are likely to be attributable to other – not immunological – factors.

The effect of HLA matching and the influence of immunosuppression

The development and use of effective medicinal anti-rejection treatment has led to considerable improvement in the outcomes of transplants involving organs from deceased donors (Cai02, Har00). Following the introduction of ciclosporine immunosuppression in about 1980, the survival of kidney, heart and liver transplants has increased greatly relative to the preceding period. More recently, new immunosuppressant drugs have further enhanced the scope for preventing and treating rejection phenomena. The ultimate goal of chemical immunosuppression is of course the elimination (prevention) of all forms of immunological transplant rejection. Against this background, it is pertinent to ask whether the availability of more effective immunosuppression has yet negated the effect of HLA matching (Su04).

3.1 Does modern immunosuppression make HLA matching unnecessary?

The development of successive generations of powerful anti-rejection drugs has greatly reduced the incidence of acute rejection (Pau99). This has led to speculation regarding the possibility that the allocation of organs on the basis of HLA matching has been rendered redundant. The rationale being that optimised anti-rejection therapy may be expected to diminish the benefit of matching for HLA tissue antigens, possibly to the point where prospective matching is no longer advantageous for the organ recipient, and may even have the disadvantage

of increasing the waiting period. Under such circumstances, prospective HLA matching could (indeed should) be abandoned.

However, it is apparent from clinical practice that immunosuppression is not yet an optimal therapy without side effects. Earlier research has demonstrated that ciclosporine A (CyA) and the monoclonal anti-T cell drug OKT3, both of which significantly reduce acute rejection, are not yet capable of eliminating the beneficial effect of HLA matching (Ope87, Ope91b, Tho92).

In recent years, a series of new immunosuppressant drugs have been developed, which are claimed to be more powerful, more selective and less harmful (to the kidney and otherwise) than their predecessors. The main drugs in question are FK 506 (tacrolimus or Prograf®), Neoral® (reformulated CyA) and MMF (mycophenolate mofetil or Cellcept®). The implications of these drugs for the effect of HLA matching have now been investigated as well. Using internationally collected data from the CTS (Collaborative Transplant Study) Registry, Opelz et al performed an analysis of transplant survival following nearly 25 000 first-time kidney transplants involving organs from deceased donors, performed in the period 1996-1999 (Ope01). In all the studied cases, anti-rejection treatment involving at least one of the new generation of drugs was used.

The analysis revealed that the donor-recipient tissue match at the HLA-A, -B and -DR loci had a major influence on transplant survival. After three years, the transplant survival rates associated with, respectively, 0, 1, 2, 3, 4, 5 or 6 mismatches were: 86, 83, 81, 80, 80, 75 and 72 per cent. In view of the large number of cases covered by the study, the differences and therefore the association between the number of HLA mismatches and transplant survival are statistically significant.

In practice, the new drugs are normally used in combination. Consequently, it was not possible to distinguish the effects of any individual immunosuppressant on the basis of the analysis. Further analysis, directed at the effects of the individual drugs, regardless of whether a second immunosuppressant was also used, yielded results consistent with those described above. The conclusion was therefore that none of the three new drugs was able to eliminate the positive influence of HLA matching on kidney transplantation.

Very similar findings were obtained by Meier-Kriesche et al when they investigated the interaction of azathioprine, MMF and HLA matching, and their effects on kidney transplant survival, by analysing data from the United States Renal Transplant Data Registry (USRDS), regarding more than 19 500 patients who had received transplants between 1995 and 1997. Three-year transplant survival was higher in MMF-treated patients than in the azathioprine group, but

in both groups the risk of transplant loss rose significantly as the number of donor-recipient mismatches increased (Mei01).

The findings set out above support the conclusion that, even with the new, more powerful immunosuppressant medication, HLA matching still has a beneficial effect, justifying the continued use of HLA matching in deceased donor kidney transplantation.

3.2 HLA matching and maintenance immunosuppression

Acute rejection and transplant survival are not the only outcomes that need to be taken into account when considering the relationship between HLA matching and the use of immunosuppression (Cic05). Another factor is the maintenance dose of immunosuppressant that the transplant recipient has to take in order to prevent rejection in the longer term. Ideally, a year after transplantation, the daily ciclosporine dose should gradually be reduced to an average of 3.2 milligrams per kilo bodyweight. However, it is known from clinical practice that the maintenance dose given to patients whose HLA match with the donor organ is not very good (more than 4 mismatches) actually has to be increased (Ope03). The same issue exists with steroids and FK 506. One may reasonably conclude, therefore, that seeking a good HLA match for the patient is important as a means of minimising the required immunosuppressant maintenance dose ('tapering'). Finally, it has been observed that HLA matching can reduce the likelihood of patients failing to adhere to maintenance medication plans and can mitigate the adverse consequences when they do. Lower maintenance medication doses are more likely to be acceptable to patients who are less inclined to follow their doctors' orders (Cic05).

3.3 The likelihood of malignancy after transplantation

Modern medicinal immunosuppressant therapy has resulted in far less acute organ rejection following transplantation. However, it is feared that prolonged immunosuppressant therapy may increase organ recipients' cancer risk (Bue05, Gon00). High doses of immunosuppressant medication, particularly over-immunosuppression where maintenance medication is taken, contribute to 15 to 20 per cent of transplant recipients developing cancer within ten years (Lut03). The most common forms of post-transplant malignancy are skin cancer and lymphoproliferative disorders, such as non-Hodgkin's lymphomas (Odo05, Ope93).

Moreover, it is believed that the HLAs themselves may play a role in the development of cancer after transplantation. Research has found that the relative risk of developing skin cancer is considerably greater in patients with one or more class I HLA mismatches (particularly HLA-B mismatches) (Bou90, Bou94). Other researchers have observed a correlation between the presence of mismatches at the HLA-B locus and the incidence of post-transplant lymphoproliferative disease (PTLD) (Bak05). One may reasonably conclude, therefore, that HLA matching can help to minimise the frequency of transplant recipients subsequently developing cancer as a consequence of taking high doses of immunosuppressant medication.

3.4 Conclusion

Since the introduction of powerful modern immunosuppressant medication, the positive effect of HLA matching appears to have diminished a little. However, careful analysis reveals that it is mainly the effect on the short-term outcomes of kidney transplantation (acute rejection) that has changed. Matching continues to have a significant effect on long-term outcomes, as reflected in greater transplant half-lives and less frequent chronic rejection. HLA matching also allows for lower immunosuppressant maintenance doses, which translates into lower costs and less risk of post-transplant cancer.

Possible correlation between HLA matching and cold ischemia time

The Minister's request for advice alludes to a possible relationship between HLA matching and the duration of cold ischemia, i.e. the length of time that the donor kidney is in cold storage between excision for the donor and implantation in the recipient. HLA matching and the allocation of donor organs on the basis of such matching (organ sharing/exchange) may lead to organs needing to be transported greater distances to the centre where the recipient is being treated. In addition, it is known from practice that prolonged cold ischemia time (CIT) has an adverse effect on the quality of the organ, sometimes resulting in delayed graft function or earlier rejection. Consequently, if HLA matching leads to more frequent long-distance organ exchange and thus to longer average CITs, the survival of transplanted organs is likely to be adversely affected. That in turn might justify the cessation of HLA matching or at least the scaling back of (international) donor organ exchange in favour of local or regional organ allocation (Asw93).

4.1 How may the problem be analysed?

It has proved difficult to study the possible correlation referred to above. The effect of HLA matching on transplant survival and the effect of CIT on graft quality and function are independent parameters. It is known that, on the one hand, a favourable HLA match generally improves the chances of transplant survival, while, on the other, prolonged CIT (more than twelve hours) has an adverse effect on the donor kidney. The question is: which effect is stronger? If

the duration of cold ischemia is the dominant factor, it may follow that minimising the CIT should be the priority and that HLA matching should therefore be curtailed. The local or regional allocation of donor organs might also be preferable to (international) exchange. However, if a good HLA match remains an important outcome determinant even when the CIT is short, there would appear to be no justification for making fundamental changes to the allocation and exchange policy.

Correlation between CIT and transplant outcome

As long ago as 1988, Opelz analysed the effects of matching-based organ exchange, and came to the conclusion that the beneficial effects of HLA matching far exceeded the adverse effects of the possible prolongation of cold ischemia (Ope88). He argued that this observation supported continuation of the established organ sharing/exchange policy. Furthermore, the previously cited research by Takemoto et al (Tak00) showed that, in the USA, average cold ischemia time did not increase when UNOS introduced an allocation policy, under which donor kidneys with no HLA mismatches (a 6-antigen match) were exchanged at the national level. On average, perfect-match donor kidneys were implanted within an average of 23 hours, regardless of whether they were allocated nationally or used locally. However, because there was no difference in CIT, the Takemoto study could not shed light on the influence of prolonged cold ischemia on transplant survival.

The UNOS allocation model outcome study was repeated in 2000 by Mange et al, this time including donor kidneys with an HLA mismatch (Man01). The researchers isolated UNOS data on 5,446 pairs of same-donor kidneys, where one kidney in each pair had been allocated to the national waiting list and the other used for local transplantation. More than 31 per cent of the exchanged kidneys were given to patients with no HLA mismatches, compared with only 4 per cent of the locally transplanted organs. There was also a considerable difference between the two groups in terms of cold ischemia time: the average for the exchanged group was 26.5 hours and that for the locally transplanted group 19.5 hours. Analysis of the effects of various variables on transplant survival revealed that both the degree of tissue matching and the cold ischemia time had a significant influence on the survival of exchanged kidney transplants, but that the two effects cancelled each other out. Following procedures involving inferior tissue matches (more than one mismatch), the rate of one-year transplant survival was lower, due to an increased likelihood of rejection. This is very likely to be related to the longer cold ischemia time, which is known to increase the

intensity of the immune response (Hel94). On the other hand, no correlation was observed between the cold ischemia time and one-year transplant survival following procedures involving no mismatches: amongst zero-mismatch recipients, a longer CIT did not lead to more acute rejection. Nor did a longer ischemia time have any adverse effect on longer-term transplant survival, either in the exchange group or in the local transplantation group. The researchers concluded that the national exchange of kidneys (which involved some increase in average cold ischemia time) had no discernible negative influence on transplant survival when a strict matching criterion (no HLA mismatches) was applied.

Similar research was carried out by Bresnahan et al in 2000, again using data from the UNOS database (Bre02). This team analysed the survival of 4770 pairs of transplanted kidneys from 2,385 donors, one of whose kidneys was allocated to a zero-mismatch exchange recipient and the other to a one-mismatch local recipient. Again, HLA matching was found to have a positive effect on transplant survival in the exchange group, particularly where the donors were relatively young, despite the greater transit distances and the consequent slight increase in average cold ischemia time (24 hours, compared with 22 hours). However, matching and exchange had no discernible benefit for African American recipients or for the recipients of kidneys from older donors (> 50 year). The researchers concluded that the benefit of HLA matching and exchange easily exceeded the disadvantages associated with increased average transit distance and slightly increased average CIT, provided that the organs were sourced from young donors (Cec02).

Similar conclusions were drawn by Morris et al from their analysis of the effect of HLA matching on nationally exchanged donor kidneys in the UK. This team reported that, where organs were transplanted within thirty hours, a longer cold ischemia time had no adverse effect, provided that there was a good or very good HLA match (Mor99).

More recently, a team of British researchers has investigated the effects of introducing a supraregional exchange programme (similar to Eurotransplant) in Scotland and Northern Ireland (Joh00, Oni02, Sud02). They analysed the survival of both exchanged and locally transplanted kidneys and assessed the efficiency of the programme (utilisation of available donor organs). It was concluded that the exchange programme had led to a 17 per cent increase in the total number of transplants, and that exchange between centres had also increased (55 per cent of kidneys exchanged prior to the programme's introduction and 78 per cent thereafter). Furthermore, the percentage of kidneys

given to zero-mismatch recipients rose from 9.5 to 21 per cent, and the two-year transplant survival from 81.5 to 88.4 per cent. Before the programme was set up, concerns had been expressed about the possibility that it would lead to longer cold ischemia times and would therefore have an adverse effect on transplant outcomes. However, the increased exchange appeared to have almost no influence on the average cold ischemia time (20 hours for locally transplanted kidneys and 22 hours for exchanged organs) and the slight increase had no repercussions for transplant survival. The researchers concluded that the main obstacles to shorter CITs were logistic (shortages of theatre capacity and personnel and overcrowded theatre programmes). As a result, kidneys given to local recipients were not implanted sooner than exchanged kidneys ('the shipped kidney is in the air while the locally used kidney sits on ice').

Of relevance in this context is the analysis performed by Opelz et al on data from the CTS database. As well as examining the possibly harmful effect of prolonged CIT on transplant outcome, the team looked at the influence of a very short cold ischemia time. The findings indicated that a very short cold ischemia time (< 12 hours) had a favourable effect on transplant survival, but that this effect was amplified by the closeness of the tissue match (Ope05). In other words, HLA matching remains valuable, even when the CIT is short. The implication is that, even in a programme which prioritises the local use of donor kidneys and minimisation of CIT, a high degree of HLA compatibility is desirable (see Figure 5).

Building on the analysis described above, Opelz studied the survival of perfectly matched kidney transplants (transplants with no HLA-A+B+DR mismatches) from both living related donors and deceased donors, in relation to variations in cold ischemia time. He found that even when the CIT was very short (< 12 hours), transplant survival was demonstrably greater in the living donor group, even though the degree of tissue correlation was the same in both groups. However, almost no such difference was discernible when the analysis was confined to procedures involving young donors in the 'ideal' age group (20 to 40-year-olds). Opelz accordingly concluded that it was not so much the cold ischemia time that mattered, but the quality of the organs.

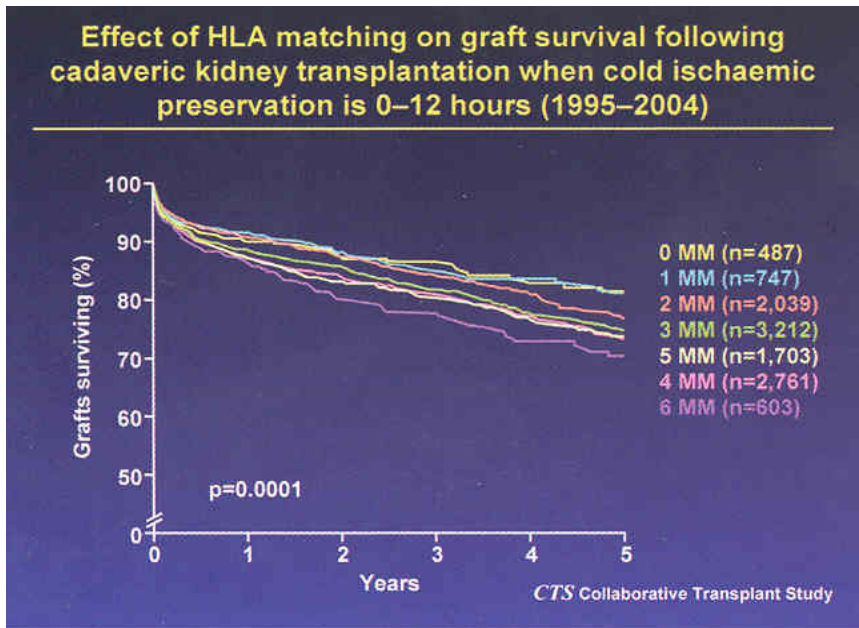


Figure 5 Effect of HLA matching on transplant survival in association with a short CIT. Source: Opelz 2005.

4.2 Conclusions

The available research data show that the exchange of donor kidneys on the basis of HLA matching has benefited recipients by reducing acute and chronic rejection and improving transplant survival. Such exchange is not associated with any substantial increase in cold ischemia time due to increased transit distances. Even when the CIT is relatively long, a high degree of HLA compatibility mitigates the effect of cold ischemic injury.

In practice, it appears that very short CITs are difficult to achieve for logistic reasons, particularly competition for theatre capacity, the limited availability of transplant teams and the need for repeat crossmatch testing. Consequently, even if shorter CITs are desirable, they are not generally realisable under the present circumstances. Furthermore, the research data currently available indicate that, even when shorter cold ischemia times are achievable, HLA matching has a beneficial influence on transplant survival.

The overall conclusion is therefore that the benefits of a good HLA match are not negated by an increase in cold ischemia time (and hence ischemic injury).

However, the effect of matching is subordinated when kidneys are sourced from an older donor (> 50 year).

For which patients is HLA matching essential?

The primary objective of a donor kidney allocation programme is to find a suitable donor kidney for every patient on the waiting list within a reasonable period of time. From the experience of the last 35 years, it is apparent that the matching and exchange of organs with a view to securing perfect or favourable donor-recipient HLA matches has significant benefits for patients, in the form of reduced rejection risk and improved transplant survival. Unfortunately, however, the structural shortage of (deceased) donors is such that it is not possible to give every waiting patient the clear benefit of a perfect match (a 6-antigen match or zero-HLA mismatch).

A national (or international) donor kidney allocation system that is based on matching and exchange therefore needs to prioritise those patients who are most likely to benefit from matching (through improved transplant survival prospects), those for whom the theoretical chance of finding a well-matched organ is relatively small, and those who might otherwise be kept waiting for an unreasonable length of time. The allocation models and procedures used by most national and international exchange programmes include arrangements to the effect described. The analysis presented in this Section of the report uses as its starting point the current Eurotransplant policy, under which organs are allocated using ETKAS, the system described earlier.

5.1 Perfectly matched patients

In all large collections of data on kidney transplant patients, there is a strong correlation between the number of HLA-A, -B and -DR mismatches and adverse transplant outcomes (acute and chronic rejection, poor long-term transplant survival). This correlation has persisted since the introduction of more effective immunosuppressant therapies. A patient whose tissue type is a perfect match with the donor (six common tissue antigens – a ‘full-house’ match), or who exhibits no HLA-A,-B and-DR mismatches, unquestionably stands to benefit more from transplantation (in the form of three to four years’ extra transplant survival) than any patient with one or more mismatches. In almost all exchange programmes, priority is therefore given to the realisation of such matches: whenever a perfect match is possible, mandatory exchange of the donor organ takes place with the centre treating the matched recipient (Mic79). In the Eurotransplant region, the exchange of perfectly matched organs remains a cornerstone of policy: since introduction of the new allocation system (ETKAS) in 1996, an average of 21.5 per cent of transplants have involved no HLA mismatches. This is a very high percentage compared with those achieved by comparable organisations elsewhere, such as UNOS in the USA, UKTS in the UK, and Établissement Français des Greffes in France.

5.2 Highly immunised patients

A proportion of the renal patients awaiting transplants will at some point in their lives have come into contact with foreign HLAs, usually as a result of pregnancy or blood transfusion, or in the context of an earlier (unsuccessful) transplant (Gor88). In consequence, these patients have blood-borne antibodies to the foreign HLAs in question (e.g. those of the child’s father or of the blood donor). If such a patient is given a kidney from a donor to whom the patient already has antibodies, violent rejection of the transplant will normally follow very quickly (Abe97, Dav94). Therefore, in order to find a suitable donor for such highly immunised patients, it is necessary to take account of the presence of donor-specific antibodies. This implies universal serological crossmatching: testing the patient for antibodies to the HLAs of a potential donor. If the crossmatch is positive (because the donor’s HLAs are incompatible), transplantation cannot go ahead. For the patient, his/her high degree of immunisation means that fewer potential donors are suitable; that in turn is liable to result in a prolonged wait.

The standard measure of immunisation is a percentage figure known as the panel-reactive antibody (PRA) level.

From the analysis of kidney transplant outcomes in large groups of patients, it is apparent that a good HLA match is particularly important for highly immunised patients (those with PRA levels > 50 per cent). In other words, the prospects for transplant survival in these patients will not be good unless an identical or near-identical donor can be found. An imperfect match (2 MM) will result in rejection and rapid transplant loss (Cla89a).

While patients awaiting their first transplant can be affected, high PRA levels constitute a particular problem where patients awaiting re-transplantation are concerned (Gje02). The rejection of a previous donor organ means that many of these patients have PRA levels of 50 per cent and above. Again, the result tends to be a long time on the waiting list, because the pool of suitable donors is limited by the patients' immunity (Tho03).

Within the Eurotransplant programme, highly immunised patients have for a long time been given priority in the allocation of organs from negative-crossmatch donors (HIT Programme). More recently, the special Acceptable Mismatch (AM) Programme has been developed, with the aim of increasing the likelihood of finding suitable donors for these patients. An 'acceptable mismatch' is defined as a mismatch entailing an alloantigen against which the patient has not developed antibodies (Cla89b, Cla99, Smi01). The AM Programme seeks to find donors who are entirely HLA-DR compatible with the patients, but exhibit an acceptable HLA-A or -B mismatch. The approach draws upon the discovery that HLA mismatches do not all trigger equally strong immunological responses – a phenomenon known as differential immunogenicity (Dan04, Dox04). Some mismatches trigger no immune response, or only a weak one (the 'acceptable mismatches'), while others produce a violent response ('taboo mismatches') (Dox96). Acceptable mismatches are associated with transplant survival rates comparable with those for zero-mismatch procedures. If a donor organ becomes available that is an acceptable mismatch for a highly immunised patient, the patient in question is given priority and the kidney is exchanged. Approximately 13 per cent of the patients on the Eurotransplant waiting list are immunised (PRA levels of at least 6 per cent). Of these, a very small proportion are highly immunised (PRA levels of 85 per cent). In 2004, twenty-five patients in this highly immunised group received transplants through the Acceptable Mismatch programme.

5.3 Patients with rare HLA phenotypes

A disproportionate number of the patients who have to wait a long time for a transplant have rare HLA phenotypes; often, these people are also homozygotic (having an identical HLA at one or more HLA loci). Many of the people concerned are ethnically distinct from the dominant population group and express HLAs or HLA haplotypes that are unknown or very rare in the population from which donors are drawn. If such patients have to wait for a perfect or favourable HLA match, it is extremely unlikely that a suitable donor will be found within a reasonable space of time, since the highly polymorphic nature of the HLA system means that very few people will have a perfect tissue match. Conventional matching for HLA-A, -B and -DR consequently implies a prolonged wait. The AM Programme has therefore been advantageous to these patients too, by seeking donors on the basis of perfect HLA-DR compatibility (see also Section 6). ETKAS prescribes the 'mandatory' exchange of donor organs for these patients, and an increasing number of them are being found help.

5.4 Patients who are recommended for priority exchange, but not on the basis of HLA compatibility

Ever since kidney transplantation began, it has been possible to prioritise highly urgent (HU) cases. A 'rescue' transplant is then performed at the earliest opportunity, with a view to saving the patient's life. In such circumstances, however, it is often necessary to set aside the normal minimum HLA compatibility criteria; a donor is considered acceptable provided that the crossmatch is negative (indicating the absence of reactive antibodies to the donor). Because of the poor or moderate HLA match, the outcome of such transplants is often disappointing: the average two-year transplant survival rate is 60 per cent. The patients who undergo rescue transplants form a very heterogeneous group and have very different backgrounds.

Within the Eurotransplant programme, the aim is to keep the number of applications for waiting list cases to be accorded HU status as small as possible (a maximum of 1 per cent of the active waiting list), in order to prevent interference with the normal allocation system. HU patients are awarded ETKAS system bonus points, so that it is more likely that they will find themselves at the top of the allocation list. The result is that most HU patients receive a transplant within four weeks. This has been beneficial mainly to child patients. Eurotransplant's policy is that, even in HU cases, a donor with no more than one

HLA-DR mismatch should be sought, in order to mitigate the risk of acute rejection and transplant loss. Such a donor is found for approximately 90 per cent of HU patients.

A second category of patient for whom exchange is recommended, but without HLA compatibility being sought, is older patients (over-65s). Partly because of the good outcomes achieved by kidney transplantation, also in older people, and the high risk of mortality amongst older dialysis patients, the number of older patients on the waiting list for a first-time kidney transplant has increased sharply in the last ten years (from 4 per cent of the ET waiting list in 1993 to 7 per cent in 2004). However, a risk analysis has revealed that, mainly because of the lower average residual life expectancy of older people, patient survival after kidney transplantation is substantially lower in this group than in younger patients (Fij01). Many older transplant recipients die with an implanted organ that is still functional (Smi96). Consequently, the survival benefit of kidney transplantation relative to dialysis disappears after approximately three years. It is also known that organs donated by older people are more likely to exhibit delayed graft function and poor subsequent survival. This is probably the result of nephron mass loss and the consequent reduction in functional reserve. For this reason, the profession has become reluctant to allocate older donor organs to younger patients. On the other hand, older donor kidneys can still function very well in older recipients, and with less risk of rejection than in younger recipients. However, HLA matching has no discernible benefit when an older recipient is given an older donor organ. In light of these observations, Eurotransplant has developed a special allocation model for older renal patients: the Eurotransplant Senior Program (ESP). In this so-called 'old-for-old' exchange programme, older patients are given kidneys from older donors (over-65s) wherever possible. The best outcomes are seen mainly amongst older non-immunised first-time recipients (Gie04). Since the introduction of this programme, the average waiting period has diminished considerably, and the outcomes have consequently improved. The existence of the Senior Program has the added benefit of meaning that the average quality of the donor kidneys given to younger patients has increased, since they no longer receive organs from older donors.

5.5 Conclusion

Allocation of donor kidneys on the basis of HLA matching contributes significantly to the goal of securing the best possible donor kidney for every patient on the waiting list, within a reasonable space of time. That contribution is

particularly important for the one in five patients for whom perfectly matched donor kidneys are sourced through the exchange programme. However, HLA matching also has major benefits for patients whose immunisation status or rare HLA phenotype makes finding a suitable kidney difficult. For such patients, matching models that identify 'acceptable mismatches' for individual patients are a workable solution with good transplant survival prospects. When an acceptably mismatched donor kidney is found for a patient in this group, it is prioritised for exchange.

Strategies for improving kidney transplant survival

The positive effect of optimal HLA matching on kidney transplant survival has been known about for more than thirty years. However, it must be recognised that in practice a perfect HLA match (no HLA-A+B+DR mismatches) can be achieved in only about 20 per cent of cases (Cla03). That implies that it is necessary to define minimum tissue-match criteria or maximum acceptable HLA mismatch criteria, in order to ensure that the other 80 per cent of patients get the next best possibility in the search for the best available match. In most kidney transplant programmes that make use of national or international allocation systems, the minimum match criterion is that donor and recipient must have at least one HLA-B antigen and one HLA-DR antigen in common (Tak94).

In recent years, a number of changes to the donor kidney allocation strategy have been proposed (and in some cases implemented), with the aim of securing suitable donor organs, good outcomes and reasonable waiting periods for more patients. The changes in question are outlined below.

6.1 Enlarging the donor pool

It is worthwhile seeking to match patients and donors on an immunological basis only if one is able to work with a relatively large pool of recipients and donors (Gje91, Mic89). A donor organ allocation and exchange programme therefore needs to operate across a large donor catchment area, so that donors can be selected from a sizeable population. The greater the number of donors, the

greater the likelihood of a good match (Mic89). In order to be successful, therefore, an allocation policy aimed at maximising the number of transplants that involve no HLA-A+B+DR mismatches ('full-house' matches) needs to have the largest possible donor pool. It has been calculated that, in the US, a local allocation policy is capable of providing an optimal match for only 2 per cent of patients. At the next level up, a regional allocation policy can achieve perfect matches for 5 per cent of patients. Finally, a national exchange (sharing) policy is capable of delivering zero-mismatch transplants to 20 per cent of patients (Mic89). A similar picture emerges in relation to patients with rare HLA phenotypes or high levels of immunisation; very few donors are potentially suitable for such patients, making the allocation of matched organs a realistic possibility only if there is a large donor pool (Tak94, Wuj93). It must be borne in mind, however, that the possibility of finding a zero-mismatch donor through an exchange programme is subject to an (immunological) limit: in a given population, perfect matches can never account for more than 25 per cent of all transplants (Ter03).

To sum up, it is desirable to continue to seek to enlarge the donor pool, even where a relatively large donor catchment area – such as the Eurotransplant region (population: 125 million) – already exists.

6.2 Prognostic transplant survival index

In 1992, Thorogood described the possible use of a prognostic index for donor kidney allocation by Eurotransplant, based on an analysis of potentially prognostic factors in kidney transplantation and statistical modelling of the long-term effects of those factors (Tho92). The following factors were proposed: number of HLA-B and -DR matches, cold ischemia time, blood group, age and gender of donor and recipient, and degree of immunisation (PRA level). Thorogood argued that these factors could be used as the basis for developing a risk score, thus enabling the identification of those patients in whom transplant survival prospects are good or bad, and helping to guide post-transplantation treatment policies. This approach has since been partially incorporated into Eurotransplant policy.

6.3 Matchability concept

Every renal patient will at some point ask, 'What are the chances of a well-matched kidney being found for me within a reasonable time?' The transplant surgeon will attempt to answer this question by referring to a 'match prognostic

index': a predictive model for calculating the relative likelihood of a particular patient being found a donor kidney with a favourable HLA match (match probability). By considering the patient's individual characteristics, such as HLA phenotype and immunisation level, the surgeon can establish the minimum HLA matching requirements and estimate how likely it is that a donor kidney satisfying those requirements will be found (Mee00).

The matchability concept is integrated into Eurotransplant's current allocation system (ETKAS), insofar as patients on the waiting list are awarded points on the basis of their chances of receiving a suitable kidney. Patients with a low match probability are given extra points in order to boost their chances of getting a transplant.

Introduction and application of the matchability index can also avoid situations arising where a patient for whom it should be relatively easy to find a good match is nevertheless given a less suitable transplant. Moreover, it prevents the waiting list becoming congested with patients who are difficult to match. The effect of the matchability index is apparent from the composition of the Eurotransplant waiting list before and after the index's introduction: the number of patients with a high matchability profile increased from 18 to 21 per cent, while the number of patients with a low matchability profile went down from 32 to 27 per cent (Mee00).

Nevertheless, the predictive value of a matchability index has its limits. For one thing, finding a match depends not only on the recipient's tissue characteristics, but also on those of the donor. Consequently, it is possible that some of a particular donor's HLAs are taboo mismatches for an individual patient, because they would trigger rapid rejection and transplant loss. This will further reduce the pool of suitable donors. The donor HLAs that are taboo for the patient should, ideally, be incorporated into the matchability index. This is difficult, however, because there is as yet no consensus as to what constitutes an unacceptable HLA.

6.4 Better prognoses for re-transplants

As indicated earlier in this report, a poor HLA match is one of the main risk factors for the recipient developing a rejection response, potentially leading to transplant loss in the short or longer term (Sch99b). In many patients, rejection after transplantation also triggers a process of 'sensitisation': the production of HLA antibodies to the donor (Pas02, Say99, Ter03, Ter04).

There is a correlation, not only between the closeness of the tissue match and the risk of sensitisation, but also between the tissue match and the degree of

sensitisation. The better the HLA match, the lower the incidence of HLA antibodies (PRA level). This effect is apparent both where HLA-DR (class II antigens) and where HLA-A, and -B (class I antigens) are concerned.

The foregoing observation is particularly important in the context of a first-time kidney transplant, because a poorer HLA match increases the likelihood of the recipient developing antibodies to the donor (immunisation), which in turn has adverse implications for the patient's prospects of a successful re-transplant. In other words, a good first-time HLA match improves the prognosis for any re-transplant that may be required if the first ends in transplant loss (Cla04, Dox04b, Tho03).

6.5 Cross-reactive antigen group matching

In the USA, debate arose in the 1990s as to whether patients with HLAs that were relatively uncommon in the donor pool were disadvantaged by an allocation system based on conventional HLA-A+B+DR matching (Tak94, Wol95). This problem affected mainly African American minority patients, since there are many HLAs that, while common in the donor pool's Caucasian majority, are comparatively rare in black prospective recipients. Other antigens are rare in white donors, but common in black recipients. To address this problem, a system of matching based on cross-reactive antigen groups (CREGs) was developed (Cro03, Tak97). CREG antigens may be described as antigens that share particular serological response patterns. Some polymorphisms on HLA molecules are common to various HLA types, meaning that HLA molecules can be placed in families or groups, on the basis of their shared epitopes. Thus, CREGs are formed on the basis of general characteristics that are recognised by antibodies and shared by numerous HLAs (broad specificities).

From retrospective analyses performed mainly in the USA, it appears that the introduction of CREG matching has been effective. Its effect translates into a better average transplant survival rate and improved prognoses, particularly for black recipients (Cro03, Laz05, McK98, Tak01a). Furthermore, reduction of the number of relevant HLA-A and -B specificities to just ten CREGs has increased the chance of finding a good match in a relatively small, local donor-recipient pool. This could potentially remove the need for exchange at the national/international level (Hol00).

In 1998, Opelz et al performed a retrospective analysis to establish what effect CREG matching would have in Western Europe. The team used data on 59 500 kidney transplants from the CTS Registry (Wuj99) and compared CREG matching with the conventional HLA-A+B mismatch system. It was concluded

that, while CREG mismatches correlated with HLA-A+B mismatches, transplant survival was dependent primarily on the number of HLA-A+B mismatches, not on the closeness of the CREG match. In other words, the positive effect of CREG matching observed in the US studies is in fact attributable to the underlying effects of HLA-A+B matching. In Europe, therefore, the introduction of a donor kidney allocation policy based on the CREG concept would actually yield poorer outcomes than the conventional HLA-A+B+DR system.

It is also important to bear in mind that, in the USA, about 75 per cent of kidney transplants involve three or more HLA mismatches, compared with only 44 per cent in Western Europe (Ope95). Consequently, average transplant survival is better in the latter patient population. Hence, there is more scope for securing improved transplant outcomes by CREG matching in the USA than in Western Europe (Sto00, Tay99).

6.6 Differential immunogenicity of HLA mismatches: HLAMatchmaker

As explained in Section 2, HLA mismatches are not all equally immunogenic and do not therefore trigger equally serious immunological rejection responses. Furthermore, the immunogenicity of a mismatched HLA is different for every patient. These findings have led to distinction being made between permissible and non-permissible (taboo) mismatches; authors in this field refer to the ‘intelligent mismatch concept’. It is this concept of differential immunogenicity that underpins a recently developed computer program called HLAMatchmaker, which is capable of predicting whether a particular HLA mismatch will or will not trigger an antibody response (Cla02, Duq01, Duq02). This test program focuses not so much on the number of HLA mismatches, but on the functional effects of the mismatches. HLAMatchmaker is now routinely used at Eurotransplant’s Reference Laboratory when testing for the existence of mismatches that are permissible for highly immunised patients in the context of the AM Programme (Cla03). It appears that donor selection on the basis of low HLA mismatch immunogenicity has considerable value in the prevention of transplant rejection or graft-versus-host reactions.

6.7 Matching at the HLA-DR-level only

The concept of ‘functional matching’ found practical expression in the research of Doxiadis et al, who investigated the possibility of performing primary matching on the basis of complete HLA-DR compatibility (Dox04b). Analysis of the Leiden University Medical Center (LUMC) kidney transplant population

showed that the presence of a full HLA-DR match (no HLA-DR mismatches) between donor and recipient was associated with a lower incidence of acute rejection responses in the first 180 days after transplantation than the presence of an HLA-DR mismatch (1 or 2 DR mismatches). An HLA-A and -B match was also associated with a lower incidence of rejection episodes, but only in the group with no HLA-DR mismatches. This HLA class I match effect disappeared completely when one or more HLA-DR mismatches were present.

The Leiden findings were confirmed by an analysis of the Eurotransplant database, which showed that a full HLA-DR match, with or without HLA class I mismatches, was systematically associated with better transplant survival than was seen in HLA-DR mismatch cases. Furthermore, in the group with one or more HLA-DR mismatches, the closeness of the HLA class I match was barely significant as a predictor of transplant survival.

These findings could form the basis for a future donor kidney allocation strategy, in which matching is initially confined to the compatibility of HLA-DR antigens (which are in any case less polymorphous than HLA-A and -B antigens), and in which less importance is attached to the presence of HLA class I mismatches. Such a system would simplify the selection of HLA-DR-compatible recipients from the waiting list. A simulation study using the Eurotransplant donor population found that a suitable HLA-DR-compatible recipient could be found in the same country for 95 per cent of the donor organs (Dox04b). Furthermore, matching at the HLA-DR level would be advantageous to patients whose ethnicity differs from that of the majority of the donor population, since HLA-DR antigens exhibit relatively little polymorphism (Rob04, Roo04).

The practical implication of matching on the basis of a full HLA-DR match would be that donor organs could nearly always be allocated at the regional or national level. That should, in principle, help to minimise cold ischemia times, transport costs and imbalances between participating countries (Ver99).

6.8 Conclusion

Various new strategies are available or have already been implemented, which have the potential to improve kidney transplant survival. All of them have an immunological basis and are intended to increase the likelihood of a favourable HLA match, or to facilitate the avoidance of non-permissible HLA mismatches. Furthermore, prioritising full (zero-MM) HLA-DR compatibility would simplify the kidney allocation procedure.

Non-immunological considerations

In addition to the immunological and medical arguments in favour of continuing to allocate donor organs on the basis of HLA matching presented above, there are a number of significant financial and practical considerations. Those considerations are set out in this Section.

7.1 Cost

Acute rejection is the most expensive complication that a patient can develop following kidney transplantation. It necessitates additional medication, often the resumption of dialysis and prolonged hospitalisation. Transplantation on the basis of favourable HLA matching can contribute to the avoidance or management of such costs, as calculations based on US circumstances confirm (Sch99a). Schnitzler et al calculated that favourable matching could result in an overall saving of roughly \$ 200 000 on the cost of a kidney transplant, calculated over a period of three years. This calculation is based on the true cost, which includes the direct treatment cost (34 per cent additional cost for a 6-antigen mismatch, compared with a zero-mismatch), and the cost saving associated with better transplant survival (> 40 per cent cost difference between a zero-mismatch and a 6-antigen mismatch). See also Figure 6.

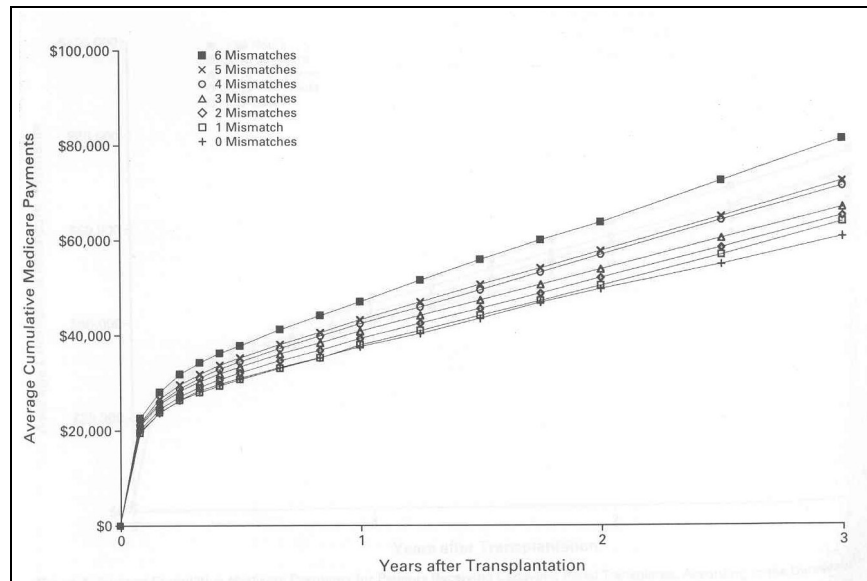


Figure 6 Average cumulative cost of kidney transplantation in the USA, according to the number of HLA mismatches. Source: Medicare 1999.

Further cost savings could be achieved by introducing or extending the exchange (sharing) of organs at the national or international level. In 1991, it was calculated that the introduction of a national allocation policy by UNOS was capable of saving the USA roughly \$ 6.5 million dollars over a period of five years, by increasing average transplant survival by 5 per cent (Gje91). However, the calculations took no account of a possible prolongation of the average cold ischemia time or the resulting ischemic organ injury. When the actual impact of the UNOS policy was evaluated in 2000, it was found that HLA matching and exchange had led to a 6 percentage point reduction in the number of rejection episodes (from 19 to 13 per cent) and that the average number of days spent in hospital in connection with a transplant had fallen from 11 to 10 days.

No similar data are available for the Eurotransplant programme, but it may be assumed that HLA matching in general, and in particular the high percentage of donor kidneys with no HLA mismatches exchanged internationally (> 20 per cent), have brought substantial savings. The more recent introduction of special matching programmes for highly immunised, homozygotic and long-waiting patients (the HIT and AM Programmes), and for children, will also have yielded economies, mainly by cutting the length of time that patients spend on the waiting list and receiving dialysis (Per01).

7.2 Objective medical criterion

Section 18, subsection 3, of the Organ Donation Act states that the allocation of available donor organs must be based primarily on medical criteria; specific reference is made to the matching of donor and recipient on the basis of their blood groups and tissue characteristics. HLA matching provides the body responsible for allocation – in the Netherlands, the Dutch Transplantation Foundation (NTS) – with an objective (medical) criterion for allocating scarce donor organs as efficiently and fairly as possible. However, the NTS is confronted by the problem that neither blood groups nor HLA groups are evenly distributed within the general population; consequently, people awaiting transplants do not all have an equal chance of receiving a suitable, HLA-matched donor kidney. As Van Rood wrote in a recent article, a key issue is how the term ‘perfect (full) HLA match’ or ‘HLA compatibility’ is defined (Roo04). He pointed out that the allocation policy in the early years was based on research into the compatibility of a total of nine HLAs, even though it was already apparent that a partial match was also associated with enhanced transplant survival. In practice, however, it has been found that a very strict policy, based on the most precise and comprehensive possible tissue typing (although this should in theory yield the best outcomes) is counterproductive for a considerable group of patients whose unusual or rare HLA types almost exclude them from transplantation. As a result, the policy came into conflict with the moral ‘requirement’ that distribution should be fair. This led to adjustment of the allocation policy, so that kidneys are now allocated on the basis of a favourable HLA-A+B+DR match, or an HLA-B+DR match only.

Recently, this definition of ‘HLA match’ has also come into question, since its application can disadvantage some non-Caucasian patient groups (Rob04). It has accordingly been proposed that the allocation policy should be based on matching exclusively or primarily on the basis of DR-locus compatibility, as recently advocated by Doxiadis (Dox04b). Over the years, others have periodically called for the complete abandonment of HLA compatibility as an allocation criterion. Quite apart from the potential impact of such a move on the incidence of rejection, average transplant survival and the side effects of immunosuppressants, it would deprive the authorities of an objective and practical criterion for allocation. An alternative, non-medical criterion capable of supporting the fair distribution of scarce donor organs is not easy to formulate.

Conclusions and recommendations

On the basis of the above analysis of the influence and effects of HLA matching in kidney transplantation with cadaver donors, the committee has arrived at the following conclusions and recommendations:

- a Despite the introduction of new, more powerful immunosuppressant drugs, retrospective analyses continue to indicate that HLA matching has a positive effect on the outcomes of kidney transplantation (less severe rejection, better transplant survival).
 - b A perfect HLA match between recipient and donor (a six-antigen match or zero-HLA-A+B+DR mismatch) gives a transplant recipient considerably better survival prospects. Transplants involving such matches should be encouraged by giving (continued) priority to the national or international exchange of perfectly matched organs.
 - c In the range that is currently normal, the cold ischemia time (the period that the donor kidney is in cold storage between excision and implantation) has no discernible adverse effect. It follows that HLA matching and exchange will remain advantageous even if they result in greater transit distances and longer cold ischemia times than if the organs were implanted locally.
 - d Eurotransplant's Acceptable Mismatch Programme has substantially reduced waiting periods and improved outcomes for highly immunised patients and patients with rare HLA phenotypes.
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- e Kidney transplants involving poor HLA compatibility (5 or 6 mismatches) should always be avoided, because they tend to have disappointing outcomes and entail a high risk of recipient sensitisation.
- f The (albeit limited) economic analyses that have been performed of the influence of HLA matching on the cost of kidney transplantation indicate that the existing matching and exchange policy brings considerable cost savings.
- g The existing matching criteria for all non-HLA-identical patients could be simplified. Simplification would lead to shorter waiting periods, more equal transplant opportunities and good outcomes for all patients in this heterogeneous group. The minimum requirement should be at least a full HLA-DR match (no HLA-DR mismatches), with HLA-A, and -B compatibility as a possible supplementary selection criterion. This could lead to fewer exchanges and thus to shorter transit distances and reduced cold ischemia times for many donor organs, as well as a better ‘organ balance’ amongst the countries participating in the exchange programme.
- h An allocation policy based on HLA matching satisfies the Organ Donation Act’s requirement that allocation should be based primarily on ‘objective medical criteria’.

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A Request for advice

B The Committee

Annexes

Request for advice

Letter reference IBE/E-2265501 from the Minister of Health, Welfare and Sport to the President of the Health Council.

Dear Mr Knottnerus,

On 26 February this year, prompted particularly by the Zon/Mw evaluation report on the Organ Donation Act, a General Meeting devoted to the topic of organ donation was held with the Parliamentary Standing Committee on Health, Welfare and Sport.

At that meeting, acting on the basis of signals received from the field, Committee members pointed out that the practical effect of the allocation criterion regarding blood and tissue matching contained in the Organ Donation Act (WOD, National Law Gazette 1996, 370) is to necessitate the transportation of donor organs to the centres where the designated recipients are being treated, which sometimes implies prolonged periods in transit – possibly longer periods than are really necessary. Indeed, it has been suggested that long periods in transit may even have a detrimental effect on organ quality.

Section 18, subsection 3, of the Organ Donation Act currently states that the allocation of available donor organs must be based entirely on the compatibility of the donor's and recipient's blood groups and tissue characteristics, the medical urgency of the recipient's condition and other factors relating to the condition of the organ or, if such factors are not decisive, on the length of time the recipient has been waiting. In other words, the existing allocation system is based upon the hitherto generally accepted assumption that ensuring the best possible donor-recipient tissue match is vitally important in relation to the transplant outcome, because it minimises the likelihood of

rejection. If, as has been suggested, the closeness of the donor-recipient tissue match has become less significant, because of the introduction of the new rejection-inhibiting drugs that are now on the market or will shortly become available, it could follow that less importance needs to be attached to tissue matching in the allocation of some organs – provided, of course, that the claimed benefits of the rejection-inhibiting drugs outweigh any adverse effects that they may have. Any change to the allocation criteria would of course have implications for the (order of) outflow of waiting list patients.

I assume that, in the report that the Health Council is currently preparing in response to my request dated 7 October 1999 (ref. CSZ/ME-633130) for advice in connection with developments in the field of organ transplantation, the question of blood and tissue matching will be covered, albeit perhaps implicitly.

However, it is my wish that, in the said report, the Council should, if possible, explicitly address the point raised by the Standing Committee regarding transit durations in relation to blood and tissue matching, and should indicate what changes, if any, the Council believes should be made to the allocation criteria contained in Section 18, subsection 2, of the Act.

Any amendments that are considered appropriate could subsequently be included in the Organ Donation Act amendment bill currently being prepared in response to the other outcomes of the General Meeting.

In view of the timetable for the amendment bill, I shall be grateful if you can advise me regarding developments in the field of organ transplantation no later than the coming autumn.

Yours sincerely,
(signed)
Dr. E. Borst-Eilers
Minister of Health, Welfare and Sport

The Committee

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- Prof. G. Kootstra, *Chair*
Emeritus Professor of Surgery, Maastricht
 - Prof. H. Akveld
Professor of Law, Erasmus University Rotterdam
 - P.J. Batavier
Transplant Coordinator, University Medical Centre Utrecht
 - Prof. I.D. the Beaufort
Professor of Medical Ethics, Erasmus University Rotterdam
 - M.E.G. van Gorp
Living Kidney Donation Coordinator, Leiden University Medical Center
 - Dr. R. Hené
Nephrologist, University Medical Centre Utrecht
 - Prof. R.A.P. Koene
Emeritus Professor of Nephrology, Nijmegen
 - Dr. G.J. Olthof
Policy Officer, Ministry of Health, Welfare and Sport
 - Dr. G.G. Persijn
Former Medical Director of the Eurotransplant Foundation, Leiden
 - Prof. M.J.H. Slooff
Professor of Hepatobiliary Surgery and Liver Transplantation, University Medical Centre Groningen
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- Prof. J.M. Wilmink
Emeritus Professor of Nephrology, Amsterdam
- Prof. J. IJzermans
Professor of Transplant Surgery, Erasmus medical Centre Rotterdam
- M.A. Bos, *Scientific secretary*
Health Council, The Hague

The Secretary to the committee prepared a draft report on the basis of a literature study and other preliminary research. This was discussed by a small subcommittee. The final draft was reviewed by the Health Council's Standing Committee on Medicine.

In the compilation of this report, the following external experts were also consulted:

- Prof. J.J. Van Rood
Emeritus Professor of Immunology, Leiden
- Prof. F.H.J. Claas
Professor of Immunology, Leiden University Medical Center
- Prof. I.I.N. Doxiadis
Professor of Immunogenetics, Leiden University Medical Center
- Prof. G. Opelz
Professor of Transplant Immunology
University of Heidelberg, Germany

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the

declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

