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MINIREVIEWS

Preimplantation HLA typing: Practical tool for stem cell transplantation treatment of congenital disorders

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Abstract

It is well known that to achieve an acceptable engraftment and survival in stem cell therapy, an human leukocyte antigens (HLA) identical stem cell transplant is strongly required. However, the availability of the HLA matched donors even among family members is extremely limited, so preimplantation HLA typing provides an attractive practical tool of stem cell therapy for children requiring HLA matched stem cell transplantation. The present experience of preimplantation genetic diagnosis (PGD) for HLA typing of over one thousand cases shows that PGD provides the at-risk couples with the option to establish an unaffected pregnancy, which may benefit the affected member of the family with hemoglobinopathies, immunodeficiencies and other congenital or acquired bone marrow failures. Despite ethical issues involved in preimplantation HLA typing, the data presented below show an extremely high attractiveness of this option for the couples with affected children requiring HLA compatible stem cell transplantation.

Key words: Preimplantation HLA typing; Preimplantation genetic diagnosis; Stem cell transplantation; Hemoglobinopathies; Immunodeficiencies; Aneuploidy testing

Core tip: Human leukocyte antigens (HLA) identical stem cell transplant is the key in achieving an acceptable engraftment and survival in stem cell therapy. However, the availability of the HLA matched donors even among family members is extremely limited, so preimplantation HLA typing provides an attractive practical tool of stem cell therapy for children requiring HLA matched stem cell transplantation.

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INTRODUCTION

Preimplantation human leukocyte antigens (HLA) matching could not be indication for prenatal diagnosis because it is not acceptable to terminate a normal pregnancy only because the foetus is HLA unmatched. However, preimplantation genetic diagnosis (PGD) for this purpose is totally different, as maximum two embryos are transferred so these embryos may be pre-selected to be unaffected one and match to affected siblings to perform HLA matched stem cell transplantation. This was first introduced in combination with mutation analysis for Fanconi anemia (FA), with a total success[1,2]. In fact FA was also the first disorder for which cord blood stem cell transplantation has been first performed[3]. FA is genetically heterogeneous group of disorders, involving different complementation groups (FANCA, FANCB, FANCC, FANCD and FANCE)[4-6], for which stem cell transplantation is the only treatment as the objective is to restor hematopoiesis which can be done only with HLA identical stem cells, to prevent severe graft *vs* host disease[7,8].

As will be described in this paper, preimplantation

Table 1 Experience in preimplantation genetic diagnosis with HLA typing

Disease	Patients	Cycles	No. of embryo transfers	No. embryos transferred	Pregnancy	Birth
Thalassemia/sickle cell disease	51	149	82	130	20	15
FANCA, FANCC, FANCD2, FANCF, FANCI, FANCJ	17	53	34	52	7	4
WAS	2	2	2	4	1	1
X-ALD	2	5	1	1	0	0
Hyper IgM	5	8	6	9	3	2
HED-ID	2	9	6	8	2	3
DBA	3	5	3	6	2	2
Krabbe	1	1	1	2	1	2
DM	1	2	1	2	1	2
Chronic granulomatous disease	1	3	3	5	1	1
Total	85	238	139	219	38	32

WAS: Wiscott-aldrich syndrome; X-ALD: X-linked adrenoleukodystrophy; HED-ID: Hypohidrotic ectodermal displasia with immune deficiency; DBA: Diamond-Blackfan anemia; DM: Dystrophia myotonica.

Table 2 Chances for detection of disease free and HLA match embryo in preimplantation HLA typing

HLA MATCH only-1/4 (25%)
Autosomal recessive or X-linked free + HLA MATCH-3/4 × 1/4 = 3/16 (18.75%)
Autosomal dominat free + HLA MATCH-1/2 × 1/4 = 1/8 (12.5%)
Autosomal recessive or X-linked free + HLA MATCH + ANEUPLOIDY-free-3/4 × 1/4 × 1/2 = 3/32 (9.4%)
Autosomal dominant free + HLA MATCH + ANEUPLOIDY-free-1/2 × 1/4 × 1/2 = 1/16 (6.25%)

HLA: Human leukocyte antigens.

HLA testing is currently applied not only with PGD for single gene disorders, but also as a sole indication.

PREIMPLANTATION HLA TYPING WITH AND WITHOUT PGD FOR SINGLE GENE DISORDERS

Our experience on PGD with HLA typing is presented in Table 1, showing that among conditions requiring HLA compatible stem cell transplantation, hemoglobinopathies are the major indication, representing the commonest autosomal recessive diseases in Mediterranean region, Middle East and South East Asia.

Hemoglobinopathies

Hemoglobinopathies, including thalassemia and sickle cell disease, are autosomal recessive disorders with abnormal production of beta-globin chains that leads to a severe anaemia, requiring a life-long blood transfusion Prevention of these disorders has been done using fetal diagnosis with reduction of new cases of thalassemia to up to 70% in many populations, including such large countries in the Eastern Mediterranean region, as Greece, Turkey and Iran[9-11]. There has been progress also in tin treatment by bone marrow transplantation[12], but this is limited due to unavailability of HLA matched stem cells, that can be overcome by PGD. We introduced PGD for thalassemia 18 years ago[13-15], and HLA typing is actually a natural extention allowing couples to produce an unaffected child as a potential HLA matched donor for thalassemic sibling.

In our experience, of a total of 293 PGD cycles for 161 couples at risk for producing offspring with hemoglobinopathies, 149 cycles were performed for HLA typing. Polar body (PB) or embryo biopsy was used to identify hemoglobinopathy mutations, and embryo biopsy was also used for HLA testing, in order to identify the embryos containing the maternal and paternal chromosomes 6 identical to the affected siblings, as described in detail elsewhere[16-18].

HLA typing was based on the methods described elsewhere[19-22]. The chances to identify unaffected embryos fully matched to thalassemic siblings is 18.75%, as for other autosomal recessive conditions, based on 25% chance of HLA match and 75% chance of having unaffected embryo (Table 2).

Of more than two dozens of different beta-globin gene mutations tested, the most frequent ones were *IVSI-110* mutation -100 cases (33%), followed by IVSI-6-39 cases, IVSII-745-23 cases, Codon 8-20 cases, IVSI-1-18 cases, and codon 39 and IVSI-5-16 cases each. Among other mutations were *IVSII-2*, *Codon 5*, *Codon 6*, *Codon 41/2*, *E121K*, -29 (A-G)-87, *R30T*, *Cap 1*, deletion 69 kb and deletion 13.4 kb. Mutation testing resulted in detection and transfer of 476 unaffected embryos (approximately, 2 embryos per transfer) in 240 (81.9%) of 293 clinical cycles, yielding 67 (27.9%) unaffected pregnancies and birth of 70 thalassemia-free children[18]. PGD for thalassemias currently represents approximately 15% of our PGD series of 2028 cases, which is the world's largest series for monogenic conditions[23].

A total of 149 of these PGD cycles were performed for HLA typing, which allowed detecting and transferring unaffected HLA matched embryos in 82 of them (Table 1). Of 824 embryos with conclusive results for testing of beta-globin gene mutations and HLA type, 602 (73.0%) were predicted to be unaffected carriers or normal, of which only 130 (15.8%) appeared to be HLA identical to

the affected siblings, which, as mentioned, is not significantly different from the expectation (Table 2)[18]. These embryos were replaced, yielding 20 healthy matched clinical pregnancies. Umbilical cord blood was collected at birth of these children, or bone marrow obtained at 1 year of age, and transplanted or pending, resulting in a successful hematopoietic reconstitution in all of them. Clearly the progress in radical treatment of hemoglobinopathies will depend on the availability of HLA identical donors[24].

PGD for HLA typing has currently been applied as an efficient tool for couples at risk in many PGD centres to ensure having thalassemia-free children who are HLA identical to the affected siblings, to serve a potential donor for stem cells for transplantation treatment. This currently is a practical tool for a use in communities where hemoglobinopathies are endemic and will improve the access to HLA matched bone marrow transplantation of these prevalent conditions.

The other large series of PGD for HLA typing for thalassemia was reported from Turkey, where 236 PGD cycles were performed resulting in birth of 70 thalassemia-free children. Of 48 affected children transplanted (in addition to thalassemia, morbid children with 9 other different conditions was transplanted), successful outcome was observed in 44 of them with a total hematopoietic reconstitution, while the graft failure occurred only in 4 of them[25-27].

Immunodeficiencies

Preimplantation HLA typing appeared to be of great utility for severe congenital immunodeficiencies (SCID), which is the key in in finding matched stem cell transplant to save live of SCID patients. Our accumulated series on PGD for SCID is presented in Table 1[28]. A total of 19 PGD cycles for 9 couples for producing affected progeny with the above conditions (this does not include PGD cycles for FA, which will be described below) were performed, including 8 cycles for Hyper IgM (HIGM), 2 for wiscott-aldrich syndrome (WAS), and 9 for hypohidrotic ectodermal displasia with immune deficiency (HED-ID). The Table 1 does not include three cases of PGD for AT and one for omen syndrome (OMS), which were performed without HLA typing, as the affected children did not survive by the time of performing PGD. PGD for OMS was the world's first case, which resulted in transfer of two unaffected embryos, yielding the birth of healthy twins. As mentioned, there was no need for HLA typing in this particular case, but the couples with previous OMS children will definitely be potential candidates for performing PGD with HLA typing to provide also an identical HLA donor progeny for stem cell transplantation. This is also highly relevant to ataxia-telangiectasia (AT), which is a progressive, neurodegenerative childhood disease that affects the brain and other body systems. A weakened immune system makes the patients susceptible to recurrent respiratory infections. Although the currently used symptomatic and supportive treatment, including high-dose vitamin regimens, physical and occupational therapy and gamma-globulin injections to supplement a weakened immune system may be helpful, the prognosis is very poor, patients still dying in their teens.

A single case PGD for AT has been reported previously for a Saudi patient with 3 affected children[29]. The disease was caused by a large deletion of more than two thirds of the *AT* gene, which was detected by amplification of one of the deleted exons (exon 19). Of three embryos available for biopsy and testing, one was a deletion free and transferred, resulting in an unaffected pregnancy.

Of 17 couples at risk for producing a progeny with FA, in addition to two carriers of IVS 4+4 A-T mutation in *FANCC* gene, three were carriers of *FANCD2*, *FANCF*, *FANCI*, *FAMCCJ*, and *FANCA* gene mutations. Overall, 52 unaffected HLA matched embryos were transferred in 34 of 53 initiated cycles, resulting in seven unaffected pregnancies and 4 FA free and HLA matched children , as potential donors for their siblings.

Five cycles were performed for X-linked Adrenoleukodystrophy, which affects the nervous system and the adrenal cortex. Of special interest is preimplantation HLA typing for HIGM, which is a rare immunodeficiency characterized by normal or elevated serum IgM levels, with absence of IgG, IgA and IgE, which results in an increased susceptibility to infections.

Of 5 couples with HIGM for whom PGD was performed, one was with C218X mutation in exon 5 of CD40 ligant gene, 3 with maternal mutations C218X exon 4 c.437_38 ins A, and one with exon 4 c.397 ins T. The maternal mutations were analyzed by PB1 and PB2, followed by HLA and aneuploidy testing in biopsied blastomeres. Of 8 PGD cycles for HLA performed, 9 unaffected HLA matched embryos were transferred in 6 cycles, resulting in 3 clinical pregnancies and birth of 2 healthy babies, as potential donors of HLA compatible stem cells for their siblings.

The first attempt of cord blood transplantation from one of the babies did not result in acceptable engraftment, so the second transplantation was performed one year later, using bone marrow mixed with the remaining portion of the cord blood sample, which provided better results in achieving successful engraftment and reconstitution of the sibling's bone marrow, and resulting in a total cure of the patient.

A total of 11 cycles were performed for WAS and X-linked HED-ID, in which 12 embryos were detected to be unaffected and HLA matched (8 for HED-ID and 4 for WAS), and transferred in 8 cycles, resulting in birth of 4 unaffected babies (3 free of HED-ID and 1 free of WAS), confirmed to be HLA matched to affected sibling.

Preimplantation HLA typing as a sole indicator

As presented in Table 3, in addition to 238 PGD for HLA cycles, 98 cycles were performed for preimplantation HLA matching without testing for causative gene. These couples were wishing to have another child anyway, but requested that if these children could become a

Table 3 Preimplantation HLA typing with and without preimplantation genetic diagnosis

Preimplantation testing	Patients	Cycles	No. of embryo transfers	No. embryos transferred	Pregnancy/birth
HLA TESTING ONLY	46	98	65	99	24/19
HLA + MUTATION	85	238	139	219	38/ 32
Total	131	336	204	318	62/51

HLA: Human leukocyte antigens.

source of stem cell transplant to save live of siblings with acquired bane marrow failures, such as sporadic Diamond- Blackfan anemia[30].

There was no difference in performing preimplantation HLA testing without PGD, except limiting the analysis of the day 3 or day 5 embryos to only HLA typing, with the sibling requiring stem cell transplantation, using a multiplex hemi-nested PCR system.

In a total of 98 clinical cycles from 46 couples performed with a primary indication of HLA typing, 99 HLA matched embryos were pre-selected for transfer. Proportion of embryos predicted to be HLA matched to the affected siblings was 21.5%, not significantly different from the expected 25% (Table 2). The transfer of 99 HLA matched embryos in 65 clinical cycles, resulted in 24 pregnancies and 19 HLA identicaldeliveries, with already available results of complete cure[30].

LIMITATIONS AND FUTURE PROSPECT OF PGD FOR HLA TYPING

A relatively high frequency of recombination in the HLA region is one of the major limitations of PGD for HLA typing, which may affect not only the accuracy of preimplantation HLA typing, but also the outcome of stem cell transplantation. In our experience, of 1713 embryos tested for HLA, 1634 (95.5%) were non-recombinant, 52 (3%) with maternal, and 27 (1.5%) with paternal recombination.. The major problem in performing PGD for HLA may be faced when the preparatory testing identified the sibling being with maternal recombination, so it could be unrealistic to identify the exact match, so the couples should be informed that only relatively close match may be possible, which may be discussed with paediatric haematologist in the pre-selection process of the embryos for transfer.

The other important limitation is that the majority of cases are in couples of advanced maternal age, so aneuploidy testing is usually an integral part of the procedure. Although the chances of pre-selecting unaffected HLA matched embryos that could be also euploid is quite low, our preliminary results of the reproductive outcome comparison between the groups of combined PGD/HLA with and without aneuploidy testing showed a significant difference. Despite transferring a lower number of embryos, the pregnancy rate was higher in the aneuploidy testing group, suggesting the potential utility of aneuploidy testing in preimplantation HLA typing, allowing the avoidance of transfer of those HLA identical embryos that are chromosomally abnormal, which are destined to be lost anyway either before or after implantation.

Therefore, patients should be properly counseled to be aware of the limits of the procedure and even lower proportion of available embryos for transfer than may have been predicted, depending also on the maternal age.

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