Willing to Cross

Guidelines

September 11, 2023

Public (P)

Canadian Blood Services

BLOOD
PLASMA
STEM CELLS
ORGANS
& TISSUES

Table of contents

Background

The Kidney Paired Donation (KPD) and Highly Sensitized Patient (HSP) programs identify transplant opportunities for patients who are waiting for a kidney transplant. However despite these registries a number of transplant candidates are unable to find a compatible donor. These patients generally have very high cPRA of ≥99.0%.

This document describes, for Transplant Programs who wish to seek additional opportunities for these patients, the guidelines and recommendations to use in identifying antigens that can be crossed.

In transplant candidates who are very highly sensitized, accepting a Donor Specific Antibody (DSA) positive, flow crossmatch negative transplant can be advantageous compared to staying on dialysis and waiting for a DSA-negative match to occur.

Consideration of which candidates are suitable for selection for willing to cross will be driven by clinical policy and transplant program discussions.

Willing to cross applies to clearly defined donor specific antigens which the transplant team considers of reduced clinical importance which when disregarded may improve the probability of transplantation

Patient Selection

The Willing to Cross Working Group (“WTCWG”) recommends the following patients be afforded the option of inclusion in this program:

1. Kidney transplant candidates with a cPRA of ≥ 99.0%.
2. The candidate has no contraindications to undergo a high-risk transplant with intense immunosuppression.
3. The candidate is enrolled in the Highly Sensitized Patient (HSP) and/or Kidney Paired Donation (KPD) programs.
4. The candidate be actively listed for kidney transplantation in the local program. Although most patients will be receiving dialysis therapies, this is not a requirement for enrollment.

5. The selection of appropriate candidates will be determined by each clinical program in consultation with their Human Leukocyte Antigen (HLA) lab.

Criteria to proceed to transplantation

The HLA lab director and clinical transplant program will approve HLA specificities to cross based on the following categories:

1. Historical antibody for the purposes of the WTC guidelines is one that is not observed in the current serum. This antibody had previously been present and was clinically relevant.
2. Low level antibody which results in a negative surrogate flow crossmatch or becomes negative upon serum dilution.

2.1. Antibody level – low Mean Fluorescence Intensity (MFI) (document normalized MFI for highest reactive bead: antigen or epitope group)

2.2. Antibody level - negative upon serum dilution (document serum dilution)

2.3. Antibody level - surrogate crossmatch negative (document serum dilution at which crossmatch becomes negative)

2.4. Antibody level - locus-specific (document normalized MFI)

2.5. Other (provide detailed reason)

When a crossmatch is performed, the Flow crossmatch is negative or clinically irrelevant (e.g., auto antibodies). If necessary, the HLA lab and clinical transplant program can consult with the WTCWG for input.

Immunosuppression

Induction

Consistent with current clinical practice, the WTCWG recommends the following induction immunosuppression:

a. Methylprednisone 500mg IV day 1; 250mg IV day 2-3

b. Mycophenolate mofetil (MMF) 1000mg or Myfortic 720mg x 1 dose within 12 hours of transplant

c. Tacrolimus (once daily dosing) 0.15-0.2mg/kg x 1 dose within 12 hours of transplant

d. Anti-Thymocyte Globulin (ATG) minimum of at least 6mg/kg over the first 4-6 days

Maintenance

Consistent with current clinical practice, the WTCWG recommends the following maintenance immunosuppression:

a. Prednisone 1mg/kg po day 4-7 then taper to 5mg daily by 2 months

b. Mycophenolate mofetil (MMF) 1000mg Twice daily or Myfortic 720mg BID

c. Tacrolimus levels 8-12ng/ml month 1; then taper to 6-8ng/ml by month 6

Treatment of Rejection Episodes

Antibody mediated rejection (AMR)

The WTCWG recommends the following treatment of AMR episodes:

a. Methylprednisone 500mg IV x 3 days; then prednisone 60mg po x 1 week then taper to 5mg daily over the next 4-8 weeks

b. Plasmapheresis minimum 6-8 sessions, daily or every other day

c. IVIG 100mg/kg after each plasmapheresis session or 2g/kg at the completion of all plasmapheresis sessions.

d. Treatment of resistant or ongoing AMR:

If creatinine does not return to baseline within 2-4 weeks following completion of treatment, consider:

i. Repeat biopsy

ii. Rituximab (375mg/m2 BSA) x 1-2 doses or Bortezomib (1.3mg/m2 BSA) x 1-2 cycles (each cycle = 4 doses)

iii. Ongoing plasmapheresis/IVIG

iv. Other treatments as per local clinical practice

v. Consult with WTCWG if necessary

T-cell mediated rejection (TCMR)

The WTCWG recommends that the treatment of TCMR episodes follow local clinical practice.

Outcome Monitoring

It is important that the following outcome data be monitored by clinical transplant programs participating in the Willing to Cross protocol:

a. DSA (de novo and pre-existing) and MFI at:

i. Day of transplantation

ii. Week 1 and 2 following transplant

iii. Serum samples should be collected at the following intervals to be stored for further testing as needed

- Month 1, 3, 6, 12 following transplant
- Yearly thereafter

iv. at time of indication biopsy

v. Clinical suspicion of rejection

vi. at time of AMR diagnosis

b. Virtual crossmatch absolute value

c. Protocol biopsy at 3 months; if done within 8 weeks no need to repeat at 3 months

d. Indication biopsy at any time point for the following reasons:

i. Development of new DSA

ii. Recurrence of historical DSA that was not present at time of transplant

iii. Significant increase in DSA; as per consultation with HLA lab

iv. If estimated Glomerular Filtration Rate ≤ 20ml/min at 6-8 weeks post-transplant and no biopsy done in prior 2-4 weeks; in absence of other predictors of poor graft function

v. Delayed graft function as per centre standard, ideally within the first 7-10 days post-transplant

vi. Any other clinically indication as per treating physician

d. Polyoma (BK)viremia in first 12 months events that required a change in clinical immunosuppression management

e. Biopsy proven AMR

f. Biopsy proven T-cell mediated rejection

g. Serum creatinine

i. week 1, 2, 3

ii. month 1, 3, 6, 12

iii. yearly

iv. at time of AMR diagnosis and 1-month post

h. Delayed Graft Function (defined as need for 2+ dialysis treatments within the first 7-10 days; excluding a single session for hyperkalemia and/or fluid overload)

i. Graft failure and cause, if applicable

j. Patient death and cause, if applicable

k. Inform Canadian Blood Services via normal business process if kidney is transplanted to unintended backup recipient

The Kidney Transplant Advisory Committee can work with clinical transplant programs to ensure that this outcome data is entered into the survey link sent by the Canadian Transplant Registry and Interprovincial Organ Sharing Program.

Safety Monitoring

To ensure optimal transplant outcomes of recipients for the Willing to Cross Protocol, the WTCWG has developed oversight measures:

a. Transplant programs must review any WTC case with the HLA laboratory on a regular basis (both pre- and post transplant)

b. All transplants and outcomes will be reviewed monthly by the WTCWG and as needed

c. Kidney Transplant Advisory Committee to review outcome data quarterly and as needed

d. If any of the below safety concerns occur, the WTC program will be undergoing review by the WTCWG.

i. Any early patient death (within first 6 months)

ii. Any early graft failure secondary to immunological reasons (within first 3 months)

iii. Any primary non function secondary to AMR

iv. Number of cases of AMR (based on Table 1a)

v. Number of kidneys allocated within HSP but transplanted to an unintended recipient because of HLA reason (based on Table 1b)

e. If none of the following are met, it would be acceptable to proceed with the next 'level' of risk transplants, as would be appropriate given patient/clinical characteristics and in consultation with HLA director

Table 1:

a) Halt and review rule based on 30% incidence of AMR and $p<0.05$.
b) Halt and review rule based on 10% of kidneys allocated in HSP but transplanted to unintended recipient thought to be due to HLA DSA and $p<0.05$

Number of total transplants performed	a) Cases of AMR	b) Cases of unintended recipient transplant in HSP Program
3	2	-
4	3	-
5	3	-
6	4	-
7	4	-
8	5	-
9	5	-
10	5	2
11	6	2
12	6	2
13	7	2
14	7	2
15	8	2
16	8	2
17	8	3
18	9	3
19	9	3
20	9	3
25	11	3
30	13	4
35	14	4
40	16	5
45	18	5
50	20	6
55	22	6
60	23	7
65	25	7
70	27	8
75	29	8
80	30	9
85	32	9
90	34	10
95	35	10

100	37	10

Example a): WTCWG review if after 5 transplants, 3 or more patients develop AMR

Example b): WTCWG review if after 10 transplants, 2 or more kidneys are transplanted into unintended recipients.

Intended Recipient Considerations:

The intended recipient who did not receive a kidney transplant because of an organ discard will remain listed in the HSP program.

Follow up process for Willing to Cross

When a transplant program discusses with their patient the transplant opportunities provided by the WTC Guidelines, the following items should be covered:

- Mandatory protocol biopsy at 3 months

  Regular testing post-transplant to provide information for the highly recommended outcome monitoring survey.

- Vaccination pre-transplant for SARS CoV2 is recommended but the WTCWG defers to local transplant program policy.

References

1. HLA Disc Doc 2016-001 – Willing to Cross Definitions
2. CTR.80.002 Willing to Cross Antigens Policy

Appendix 1: Draft patient information

Why is your doctor suggesting you proceed with this transplant?

People in the HSP program with a cPRA of 99% or higher waited about 22 months on average to get their first kidney transplant. If we remove antigens that haven't shown up in tests from your cPRA, it might be easier for you to find a match. People with a cPRA of 98% waited less than 9 months, and those with a cPRA of 97% waited less than 6 months for their transplants in the HSP program.

In the KPD program, the waiting time depends on things like how well their donor matches with other candidates and the number of people in the program. Still, a high cPRA makes it harder to get a transplant. Only 7% of people with a cPRA of 100% and 31% of people with a cPRA of 99% have received a transplant, while 63% of people with lower cPRA values have been transplanted. Compared to those with a cPRA of less than 99%, people with a cPRA of 99% waited more than twice as long, and those with a cPRA of 100% waited three times as long on average to get a transplant in the KPD program.

What are the recommendations for accepting an organ through the Willing to Cross Guidelines (immunosuppression/biopsy/data capture)?

To get the best results from your transplant, you will need to have regular follow-ups. You will need to come in for blood tests often to check your antibody and creatinine levels. Three months after your transplant, a kidney biopsy will be done to make sure there is no damage to the kidney from antibodies that did not show up in tests.

What are the risks/benefits?

Getting a transplant sooner means spending less time on dialysis, which is a good thing. But this benefit must be balanced against the risk of your body rejecting the new kidney if you had antibodies to the donor in the past. If your doctor thinks you should go ahead with a WTC transplant, the benefit of getting off dialysis might be greater than the risk of rejection.

Appendix 2: Willing to Cross Working Group members (WTCWG)

CBS Members:
Jaskiran Ubhi
Fatima Dharsee
Darlene Jagusic
Charles Wilson

Clinical working group:
Dr. Rahul Mainra (Chair)
Dr. Michel R. Pâquet
Dr. Eric Wagner
Dr. Trish Campbell
Dr. James Lan
Dr. Christine M Ribic
Dr. Khaled Shamseddin
Dr. John Gill

Appendix 3: Sample WTC Consent form (Dr. James Lan)

The Willing to Cross program was piloted in BC, this program was led by Dr. James Lan, transplant nephrologist and HLA Lab director at Vancouver General Hospital.

Dr. James Lan is also a member of Canadian Blood Services Kidney Transplant Advisory Committee, co-chair of the National HLA Advisory Committee (NHLAAC), and member of the sub-working group formed from NHLAAC which is the Willing to Cross Working Group.

Dr. James Lan has generously shared the consent form developed as a part of the WTC pilot program in BC. This patient consent form is shared in support of programs who wish to seek more transplant opportunities for their very highly sensitized patient population.

The patient consent form included in in the WTC guidelines document is for programs to use as reference or guidance when created a local patient consent form for WTC patients in their transplant program. This patient consent form can be used and modified in any way to help transplant programs and acts a resource for Transplant Physicians to would like to develop a WTC patient consent in their local transplant program. Please find consent form below:

Willing to Cross Clinical Program Consent

Introduction

You are invited to participate in this new Willingness to Cross Clinical Program which is currently piloted in British Columbia. A pan-Canadian Willing to Cross program which has a similar design to the BC Willing to Cross is expected to launch at a later date. The Willing to Cross program is designed to improve the chances of finding a compatible kidney organ for “highly sensitized” patients - those who are difficult to match due to their broad range of anti-HLA antibodies.

Background

Sensitization is a process by which the immune system is triggered to make antibodies (proteins produced by the immune system) against foreign molecules. This can happen through pregnancy, blood transfusions, and previous organ transplants. In the context of transplantation, these antibodies are called donor-specific antibodies (DSA) when they target the donor organ. DSAs can lead to rejection and an increased risk of premature graft loss. Thus, standard kidney transplantation in Canada only takes place when the patient has no detectable antibodies against the donor. Although this practice safeguards against early rejection, patients who have been sensitized to make a broad range of antibodies (highly sensitized patients, HSP), have a

difficult time finding compatible donors. Compared to patients who do not make HLA antibodies, highly sensitized patients experience prolonged waiting time and may develop dialysis-related complications while they wait for a compatible organ.

In order to improve access to transplant for these difficult-to-match patients, the BC kidney transplant program has launched a local Willingness to Cross (WTC) clinical program for those who are considered extremely highly sensitized, defined as those who are predicted to match <1% of the donor pool. Under this new kidney program system, eligible WTC patients are allowed to be transplanted across known antibodies against the donor that are deemed to have acceptable risk by their physicians. The WTC program is designed to improve highly sensitized patients' chances of finding a matched organ, but there may be an increased risk of rejection compared to standard transplants. The true risk of rejection in the context of WTC program is unknown, but it is expected to be somewhat higher than the risk associated with standard kidney transplantation. Because of the potential increased risk of rejection, patients transplanted under the WTC program will undergo enhanced surveillance testing for anti-HLA antibody and protocol kidney biopsy in addition to standard kidney transplant monitoring based on blood and urine tests.

The safety of this new WTC program is also monitored carefully by the BC Kidney Transplant Program – the outcomes of WTC patients are continuously captured and analyzed in real-time. If more than 30% of patients unexpectedly experience rejection due to donor-specific antibodies within the first year after transplant, the WTC program will be paused and undergo enhanced review to determine the appropriate changes to the protocol before more patients can be enrolled.

Your Participation is Voluntary

Your participation is entirely voluntary. You have the right to refuse to participate in this clinical program. If you decide to participate, your decision is not binding and you may choose to withdraw from the program at any time without any negative consequences to the medical care, education, or other services you may receive from this clinic or this hospital. If you decline participation in the Willing to Cross program you will continue to remain active in the Canadian Highly Sensitized Program.

Extra Testing Required in the WTC Program

1. Protocol HLA antibody testing: within 1st week, 2nd week, 1 month, 3 month, 6 month, 1 year, and annually for 5 years

2. Protocol kidney transplant biopsy: 3 month

Potential Treatments Should Antibody-Mediated Rejection Occur

- High dose corticosteroid

- Thymoglobulin
- Plasmapheresis
- Rituximab
- IVIG

Potential Adverse Effects of Rejection Treatment

High Dose Corticosteroid

High dose corticosteroid aims to dampen inflammation in the kidney and suppress the immune system. Side effects include mood changes, worsening diabetes control or new onset diabetes, appearance change with fat redistribution, stomach ulcers, suppression of immune system and increased risk of infection, and rarely avascular necrosis (may require joint replacement).

Thymoglobulin

Thymoglobulin aims to reduce the T cells (immune cells) in your bloodstream to reduce inflammation in the kidney and suppress the immune system. Side effects include low white blood cell count, low platelet count, reactivation of dormant viruses in the body, infusion reactions of fever, low blood pressure, fluid overload. Rarely, infusion reaction due to thymoglobulin may lead to profound low pressure which requires medical support in the Intensive Care Unit (ICU).

Plasmapheresis

Plasmapheresis procedure involves exchanging patient's blood plasma with albumin from pooled donor source in an attempt to decrease the burden of anti-HLA antibodies in patient's blood which are causing rejection. This procedure is associated with minimally increased infection risk, potential bleeding, and the rare scenario of severely low blood pressure which requires medical management in the ICU.

IVIG (intravenous immunoglobulins)

IVIG is immunoglobulin (antibody) infusions from pooled donors, in an attempt to reduce the HLA antibody production by my immune cells. Side effects associated with IVIG include nausea, vomiting, fevers, hives, and the rare scenario of severely low blood pressure which requires medical management in the ICU.

Rituximab

Rituximab is a medication which targets a type of immune cells (B cells) which produce HLA antibodies. Infusion reactions related to rituximab may include fever, low blood pressure, fluid overload. Rarely, infusion reaction due to rituximab may lead to profound low pressure which

requires medical support in the Intensive Care Unit (ICU). Patients receiving rituximab have a weakened immune system and are more susceptible to infections. A rare but severe brain problem called progressive multifocal leukoencephalopathy (PML) has happened with this drug which may cause disability or death.

The above has been explained to me by Dr _____. I understand that I am participating in the WTC program in order to increase the chance of finding a donor kidney. I am willing to accept the potential increased risk of rejection and treatments side effects.

_____

Patient Signature

_____

Printed Name

_____

Date

_____

Witness Signature

_____

Printed Name

_____

Date

_____

Most Responsible Physician Signature

_____

Printed Name

_____

Date