



## ORGAN TRANSPLANTATION: A HOPE OF SURVIVAL

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### ABSTRACT

Organ transplantation is only the hope of the survival for the patient suffering from life threatening diseases such as heart and liver diseases. Today Organ transplant is A major area of research for the physician. Organ Transplantation provides new life to the patient but some complication like graft reject reaction are very common from the organ transplant and that can be minimized by using a close donor and suitable immunosuppressant drugs. The Availability of the organ is another problem associated with organ transplant that can be minimized using artificial organ, Animal organ, stem cell and aborted fetus. The Major Organ transplanted are Kidney, Liver, Heart, Pancreas, Cornea, Lungs etc. Newer Immunosuppressant drugs cause a dramatic change in organ transplant because they minimize the Graft-Reject reaction and Improves the quality of life. The following article covers complete description about organ transplant, types of transplant, Graft-Reject reaction and its treatment etc.

**Key words:** Rejection, Immunosuppression, Xenograft, allorecognition etc.

### INTRODUCTION:

Recent advances in the surgery provide a treatment of serious diseases and Organ transplantation is one of them. Organ transplant can be defined as the transplant of a living tissue or organ to a diseased or ill person to restore the health and reduce disability. Organ transplantation improves the quality of life, and reduce morbidity and mortality. In these days the organ transplants are safe procedure and considered as a most accurate treatment option for thousands of patients suffering from life threatening diseases like renal failure, heart disease, respiratory disease and cirrhosis of the liver<sup>1,2</sup>. One of the greatest achievement of modern medicine through organ donation thousands of people gives a new lease of life through the people who gives their organ for saving the life of others<sup>3</sup>. In the past the organ transplant success rate is very small but due to the development of new immune suppressing drugs success rate is increased rapidly.

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The success rate of the organ basically depends upon

- Type of the organ
- Disease of the patient which cause organ failure
- Number of organs that are transplanted
- Immune system of the patient
- Relationship between the donor and recipient
- Patient care

### Types of transplant

#### Autograft

This is the transplant of one to oneself. In this type of transplant tissue transplanted from one part of the body to another in the same individual like in skin transplantation.

#### Allograft

Most of the Human transplants are of this type. Allograft is a transplanted organ or tissue in genetically non identical member of the same species for example A transplant of organ from one person to Another. Allograft is also known as anallogenic graft or homograft.

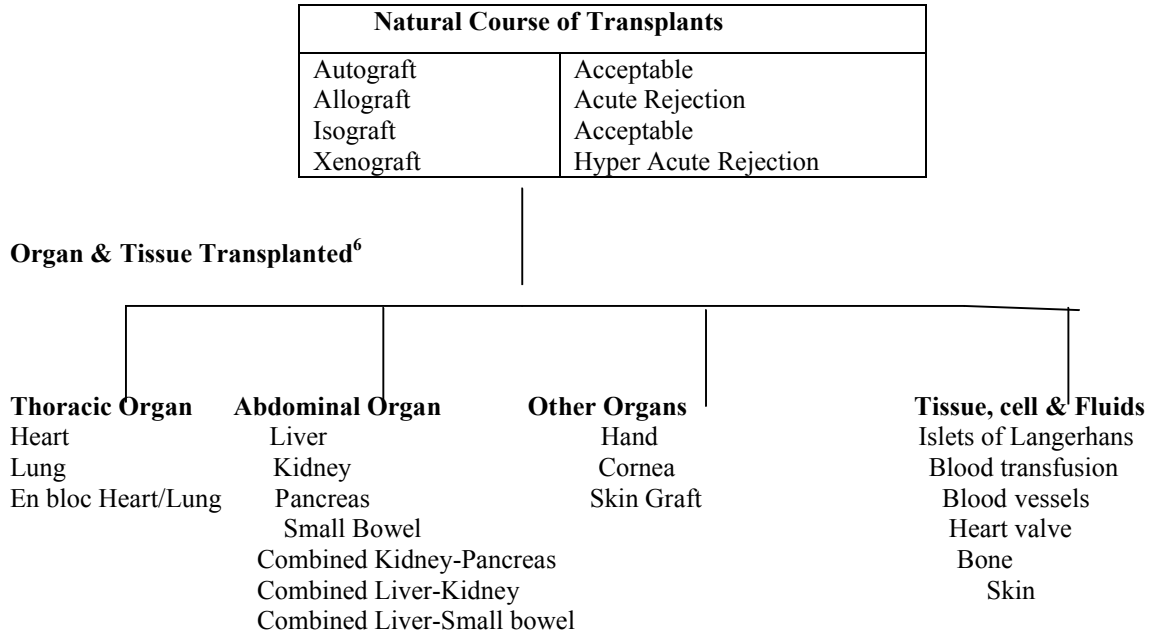
#### Isograft

Isograft is a transplanted organ or tissue in genetically identical donor to the Recipient like in identical twins. Isograft is also known as isogeneic and syngeneic grafts. It is differentiated because it is anatomically identical to allograft but it is closer to Autograft in terms of immunology.

**Xenograft**

A transplant of organ or tissue from one species to Another means the donor and recipients both are belongs to different species<sup>4</sup>. Xenotransplant is most suitable to eliminate the problem of organ shortage. Humoral immunity seen

earlier after the xenotransplantation followed by T-cell mediated cellular Immunity. In xenograft the Hyper acute rejection reaction are very common and often occur by activation of antibodies and complement. An appropriate Immunosuppressive regimen can prolongs Xenograft survival<sup>5</sup>.



**Tissue Matching**

Tissue matching of the donor and recipient is one of the most important requirement. The immune system normally attacks the foreign tissue of the body this reaction is called as Rejection. The Rejection can be minimized by choosing the most compatible(Close in Relation) member of the family means the experts are trying to find the donor whose tissue are closely matched to the recipients.

using immunosuppressive drugs. Current and future trends in immunosuppression for solid organ transplantation are focused to minimize the immunosuppressive therapy. Long term immunosuppressive therapy can cause a number of infection and other type disorders<sup>8</sup>.

**Suppression of the immune system**

In organ transplantation the immune system of the recipient mounts a highly destructive, sustained and specific attack on the transplant through recognition of foreign antigen and activation of T-cells and causes expansion of donor reactive lymphocytes and infiltration of allograft with effect or lymphocytes. Immunosuppressive drugs are required to prevent the immune system for destroying the transplant. Basically all immunosuppressant act by inhibiting T-cell Response<sup>7</sup>. The use of the Immunosuppressive drugs has significantly decreases the rate of acute rejection. Acute rejection rate decreases significantly with increase in allograft survival rate upto 50% by

**Rejection**

The recipient body recognize all grafts as a foreign antigen and initiates the immune system to remove or destroy the transplanted graft this type of reaction is called as graft reject reaction. The ability of the recipient T cell to recognize the donor derived antigen this is called as allorecognition, it initiates allograft rejection. Once the T cell of the recipient activated then they undergo expansion, differentiated rapidly and migrate into the graft where they promotes graft destruction<sup>9</sup>.

In rejection process first of all Antigen presenting cell triggers CD4 & CD8 Cells, Results in activation of both systemic and local immune system. After that cytokines activates nonspecific cells and accumulate in graft that causes development of specific T cells, Natural killer cell and the allograft destruction is started<sup>10</sup>.

### Symptom of Transplant Rejection<sup>11</sup>

Organ Transplant	Possible Symptom of Rejection
Heart	<ul style="list-style-type: none"> <li>• Shortness of breath</li> <li>• Flu-like symptoms</li> <li>• Abnormal heartbeat</li> </ul>
Kidney Or Kidney/Pancreas	<ul style="list-style-type: none"> <li>• Pain or tenderness</li> <li>• Flu-like symptom</li> <li>• Decreased urine</li> <li>• Sudden weight gain</li> </ul>
Liver	<ul style="list-style-type: none"> <li>• Yellowing of the skin or eyes</li> <li>• Itching</li> <li>• Dark urine or light-colored stools</li> <li>• Sudden tiredness</li> </ul>
Lung	<ul style="list-style-type: none"> <li>• Chest pain</li> <li>• Dry cough</li> <li>• General ill feeling</li> </ul>
Intestine	<ul style="list-style-type: none"> <li>• Diarrhea or change in stool patterns</li> <li>• Abdominal swelling or pain</li> <li>• Weight loss, poor appetite</li> <li>• Bloody stools</li> <li>• Flu-like symptoms</li> </ul>

Novel Immunosuppressant	Mechanism of Action
Tafocitinib (CP-690550)	Janus Kinases play an important role in cytokine-driven lymphocyte activation. Tafocitinib inhibits Janus Kinase Activity and produce Immunosuppressant effect.
Sotrastaurin (AEB071)	Sotrastaurin inhibits Protein Kinase C which play an important role in T cell activation and also play a crucial role in production of inflammatory cytokines including IL-2 & Interferon $\gamma$ .
Bortezomib	It is a reversible inhibitor of the 26S proteasome. The proteasome degrades ubiquitinated proteins and playing an important role in maintaining Homeostasis.
Belatacept	Belatacept is a novel biologic fusion protein composed of non-binding portion of IgG fused to the extracellular domain of cytotoxic T-lymphocyte antigen 4 that further prevents T cell activation.
Alefacept Eculizumab	Alefacept is a dimeric Humanized fusion protein that acts on CD2 receptor present on T lymphocyte & inhibit CD2-lymphocyte-function associated antigen-1 interaction.  Eculizumab is a recombinant humanized monoclonal antibody specifically binds, with high affinity, to the complement component and prevents the formation of terminal complement complex.

Type of Rejection	Time of Onset	Cause/Reason	Response
Hyperacute	0-24 hours	Preformed antidonor antibodies and Complement	B-cell-humoral
Accelerated	1-5 Days	Reactivation of sensitized T cells	T-cell-cellular
Acute	7-21 days	Primary activation of T cells	T-cell-cellular
Chronic	>3 months	Both immunologic and non-immunologic Factors	Humoral /cellular

## Type of Graft reject Reaction

### 1. Type of the Graft Rejection According to the time course

#### • Hyperacute Rejection

Immediate destruction of the graft by preformed antidonor antibodies and complement system within 0 to 24 hours. This is occur due to ABO mismatched Organ. The donor and recipient should be ABO compatible so the serum of the donor and recipient should be checked out before transplantation. Hyperacute rejection of the allograft occurs very rarely in these days, because before the transplantation it is ensured that they have not been sensitized against the graft. In recent development of the transplant xenotransplantation is one of the future scope for the transplantation and for the success of xenotransplantation Hyperacute rejection should be overcome or minimized by using Immunosuppressant drugs<sup>12</sup>. Hyperacute Rejection the transplant procedure ends with the removal of the graft. This problem can be overcome by using cross matching technique that can detect donor specific antibody before the transplant.

#### • Acute Rejection

It generally occurs within a few days of the transplant. it is due to reactivation of the sensitized T cell. It is a reversible process and can be reversed by using antibiotic and Immunosuppressant drugs<sup>13,14</sup>.

#### • Chronic Rejection

Chronic rejection can be defined as an Immunological injury to the graft which occur after severe or persistent acute rejection that results in irreversible loss of the graft. Chronic rejection is expected in the patient that have previous history with acute rejection. This is the end stage of after unresolved acute rejection or multiple acute rejection. Organ undergoing chronic rejection shows many of the symptoms like healing wound including fibroblast, endothelial cell or epithelial cell proliferation and collagen deposition within the graft. recent studies shows that the incidence of chronic rejection is decreases in past years. The large multicenter studies with the drug Tacrolimus shows the incidence of chronic rejection 1.5 to 3.0%. The most recent treatment of the chronic rejection are Tacrolimus and Mycophanolate Mofetil Immunosuppressive drug. Early treatment of the Chronic rejection can reverse it<sup>15</sup>.

### 2. Graft Vs Host

Graft Vs host disease is the cause of mortality and morbidity after allogenic hematopoietic cell transplantation. In graft Vs host disease the T cell of the donor fight with patient organ & tissue results in reducing the ability to work. Some factors are important in case of Graft Vs host disease.

- Unrelated donor transplant
- Mismatched transplant
- Female to male mismatched transplant (Female donor T cell can recognize chromosomes of male)
- Age of donor
- Effect of pregnancy
- Racial mismatch
- Condition of the recipient

There are two types of Graft Vs Host disease

- Acute Graft Vs Host Disease  
It occurs generally within a few days after the transplant. It is graded as mild to severe.
- Chronic Graft Vs Host disease  
It can occur in any of the body part but most commonly it occurs in skin, Gut and Liver.  
Graft Vs Host rejection can be treated with corticosteroid therapy and by using cyclosporine and tacrolimus. Antithymocyte globulins are also effective<sup>16,17,18</sup>.

### 3. Antibody mediated rejection

Antibody mediated rejection is an important cause of acute and chronic allograft rejection. On the basis of acuity and severity the antibody mediated rejection can be classified as follows.

- Hyperacute Antibody Mediated Rejection  
The occurrence of this type rejection are very rare due to adoption of pretransplant cross matching. The symptoms are characterized by severe endothelial and arterial injury, interstitial edema, cortical necrosis etc.
- Acute Antibody mediated rejection  
It is characterized as graft dysfunction manifesting over days. Acute antibody mediated rejection occur within 5 to 7% of all transplants. The identification of these antibody mediated rejection are easier with the development of CD4 staining in biopsy.
- Chronic Antibody mediated rejection  
In the early stage of chronic mediated rejection there are no sign and

symptoms are noticed, But in advanced stage Proteinuria, hypertension and allograft dysfunction are recorded. Furthermore it can cause Graft failure after few months.

Treatment of Antibody Mediated Rejection

- Removal of antibody by plasmapheresis, Immunoabsorption, Intravenous Immunoglobulin, and splenectomy
- Blockage of B cell proliferation by splenectomy, Cyclophosphamide, Anti CD20 etc.
- Anti plasma cell therapy eg .Bortezomib
- Use of Antithymocyte globulin that decreases T cell count
- Complement Pathway inhibitor eg.Eculizumab<sup>19,20</sup>

### Mechanism of Rejection

Rejection is basically occurs due to preformed Antibodies against the Major Histocompatibility complex (MHC) class I encoded antigen. Acute allograft rejection is initiated by large number of T cell of the recipient that recognizes alloantigen. Acute cellular rejection is graft specific form of immune rejection. Biopsy analysis of the tissue shows infiltration by host T cell followed by damaging effect on the graft. CD4<sup>+</sup> & CD8<sup>+</sup> both participates in cellular rejection but the rejection response is elicited by CD4<sup>+</sup> cells. Natural killer(NK) cells are also present in allograft during graft rejection. NK cells recognize alloantigen and constitutively express inhibitory receptors that are specific for self- MHC class I antigens. There are basically 2 process for all recognition. In the direct pathway T cell recognize intact MHC on the surface of the donor cell, and in Indirect pathway T cells recognize processed alloantigens in the context of self-Antigen presenting cell(APC)<sup>21</sup>.

### Future approaches in Rejection Treatment

- **Novel Immunosuppressants**<sup>22</sup>  
It is well known that Immunosuppressant drugs used in present causes a number of toxicity so they do not provide a proper treatment for prevention of the graft reject reaction. New agents are developed in this category to minimize the side effect with improved efficacy.
- **Acute phase protein in Transplant**  
Acute phase protein has an important value in homeostasis of cell. Acute phase protein used to diagnose the transplant rejection. Acute phase protein used to distinguish various posttransplant complication like

inflammation and arteriosclerosis. Acute phase protein can easily distinguish the feature between viral or bacterial infection & transplant rejection, that is a very difficult task and required to be detected before the treatment start<sup>23</sup>.

- **Graft Rejection treatment with IL-1 Receptor Antagonist**

Increasing in the level of IL-1 receptor causes antigen presenting cell aggregation and neutrophil infiltration that leads in inflammation. Antagonising the biological activity of IL-1 leads to increase in graft survival. IL-1 increases the time of graft transparency by inhibiting IL-1 and local neovascularisation. The IL-1 receptor antagonist are more effective in corneal transplant<sup>24</sup>.

- **Role of Thymoglobulin in Graft Rejection**

Thymoglobulin is a polyclonal antibody which is used for prevention and treatment of graft reject reaction. Thymoglobulin is used mostly for treatment of vascular, steroid resistant and antibody mediated rejection. Thymoglobulin induces lymphocyte depletion in the peripheral blood by complement dependent cell lysis. Lack of nephrotoxic property of thymoglobulin is very useful induction therapy during the early days of the transplantation. Thymoglobulin are most effective in Renal transplant<sup>25</sup>.

- **Antiinflammatory treatment strategies for transplant**

Inflammatory reaction influence the solid organ allograft, Inflammatory reaction in the graft have a pivotal influence on acute and long term graft function. Inflammatory reaction includes rejection episodes, infection and ischaemia/reperfusion(I/R) injury. I/R injury associated with acute rejection episodes affects long term graft outcome. I/R injury can be treated by blockade of cytokines/chemokines, adhesion molecules, NF-κB, specific MAP kinases, metalloproteinases, induction of protective genes, and modulation of the innate immune system.<sup>26</sup>

### Alternative organ sources

There are a lot of number of people that requires organ for their life and to fulfil the requirement of organ several alternative sources are required and some of them are given below.

- **Animal Organ**  
 Baboon hearts and pig liver are the most common organs that are used in the past and A lot of studies are required to make them effective without serious rejection. The major drawback of this type of organ that a number of bacteria enters in human body with the transplanted organ.
  - **Artificial organ**  
 Artificial organ are potential source to revert the problem of organ deficiency. The artificial organ are very costly, their effectiveness is not so well and people with artificial transplant requires further surgery if there is problem with transplant.
  - **Stem cells**  
 It is the hope of many researcher that stem cell can grow in a organ or in a group of cells. The most potent stem cell can be found from human embryo. but after the removal of stem cell embryo is destroyed so number of people found objection on this type of research.
  - **Aborted Fetuses**  
 Aborted fetus are proposed source of organ. It is more appropriate to use organ from a fetus aborted in late pregnancy and that can save the life of a person whose life in danger. It is also objectionable from the number of people<sup>27</sup>.
- Living with an organ**  
 After the organ transplantation A number of complication are to be faced by the patient but they can minimize or prevented by using some of precautions.
- Take Balanced diet
  - Doing exercise regularly
  - Make Mind stress free
  - Proper medication treatment with regular check up
  - Get support with Family<sup>28</sup>

### Organ Transplant in India

In India the treatment option are resource consuming, limited and expensive so the organ transplant is the dream for the majority of the people suffering from life threatening diseases. The prevalence of chronic renal failure in India varies from 0.78 to 1.39% and due to high cost of dialysis both haemo and peritoneal only about 10% of the total patient receives Renal replacement therapy (RRT).The most common cause behind of this is organ shortage, In foreign country cadaveric organ fulfil the requirement but in India less than 2% cases cadaveric organ are used. One of the important point is the nonexistence of near organ tracking and retrieval organisation and not involvement of transplant co-ordinators in India. A lot of people are suffering from liver disease and they can only

survive after liver transplantation. In the absence of the liver transplantation a majority of the people dies. Bone marrow transplantation and stem cell transplantation are performed in selected centre in India, the most important thing is that the cost of this type of transplant is much lower than developed country. A number of centres are in progress to improve the bone marrow transplantation in India<sup>29</sup>.

### Future Prospective

Today the field of organ transplantation increases very rapidly. Organ transplant saves the life of a number of people. The main problem is the availability of the organ that can be minimized by finding an alternate method by using artificial organ, cadaveric organ, using xenograft etc. Foreign country also collaborate with different agency that provide organ upon requirement , same thing is also needed in India to fulfil the requirement. A lot of work is required to improve the Graft acceptance and by minimizing the rejection after organ transplant. Use of newer Immunosuppressant drugs can minimizes the rejection so improve the quality of the drug can minimize the Rejection.

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