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Value of Medicine in Solid Organ Transplantation

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Executive Summary

- Solid organ transplantations have been performed for decades, with the first kidney transplantation occurring in 1954; however, early transplants were associated with poor outcomes due to organ rejection and graft loss.[1]
- Over time, improved surgical techniques, regulatory advances, and new medications increased the viability of solid organ transplantation and associated outcomes.[2,3]
- The advent of immunosuppressive therapies made possible the success and durability of solid organ transplantation as a consequence of improved clinical outcomes associated with a lower incidence of acute rejection.
- In the absence of viable organ transplantation, numerous conditions that end in organ failure would have death as their inevitable outcome.
- Compared to historical treatments and temporizing options such as dialysis, solid organ transplantation has improved overall life expectancy, clinical outcomes, and quality of life (QOL) for patients with end-stage organ disease.[4-6] This would not be possible without the existence of medications to suppress the immune system.
- Today's immunosuppressive therapies are integral and invaluable to making positive, long-term, sustained transplantation outcomes a reality.

More than 700,000 patient lives have been saved and improved through solid organ transplantation and immunosuppression[7]

Key Takeaways

Solid organ transplantation has evolved significantly over 6 decades, profoundly changing the prognosis and therapeutic landscape for patients with end-stage organ disease

Without the introduction of the current-generation immunosuppressant drugs, end-stage organ disease would still be associated with extremely poor patient outcomes and high mortality rates

Transplantation success and overall survival for patients receiving a solid organ transplant have significantly increased with the introduction of immunosuppressant drugs in the 1980s and in the 1990s

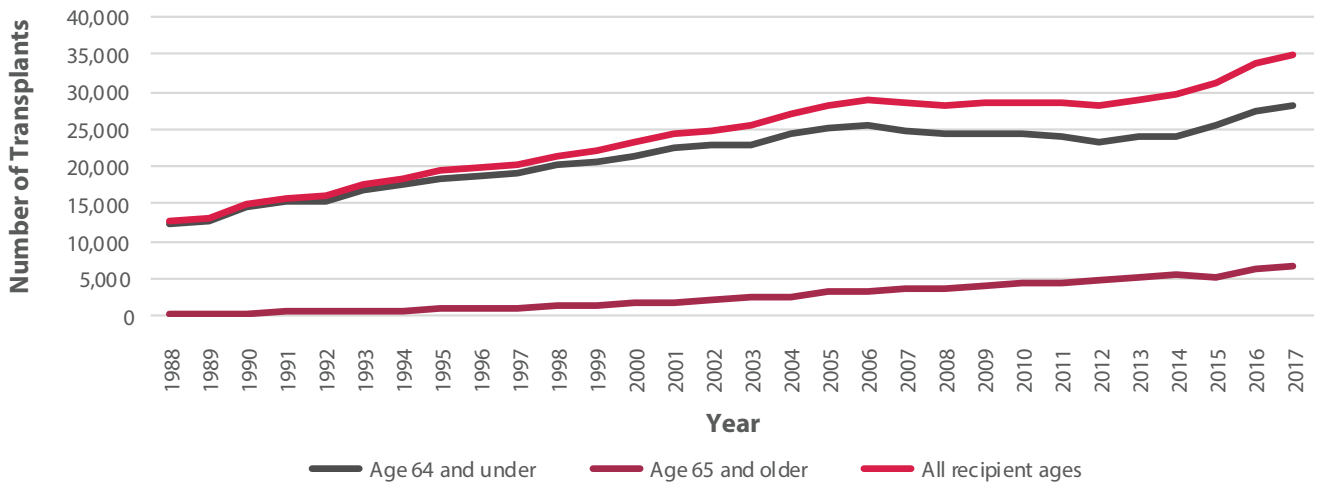
The value of immunosuppressant medicines in solid organ transplantation cannot be overstated or detached from the transplantation procedure itself; the two are integrally connected

Consistent and appropriate immunosuppression in organ transplantation can result in lives saved and overall cost-savings following transplantation

Epidemiology and Mortality of Solid Organ Disease

Over the past several decades, solid organ transplantations are estimated to have saved and improved the lives of more than 700,000 individuals in the United States (US).[7] Indeed, more than 34,000 transplantations were performed during 2017 alone.[8] The availability of immunosuppressive therapies to prevent graft failure and retain graft function[5] has resulted in tens of thousands of successful solid organ transplantation in the US each year (Figure 1). The introduction of immunosuppressive therapies has also been vital to clinical, economic, and QOL outcomes associated with solid organ transplantation. End-stage liver disease, previously an almost universally fatal condition with no alternative treatment options, now has 5-year survival rates as high as 80% with the availability of a liver transplant[4] and appropriate immunosuppressive therapies. Kidney transplant recipients can expect to live an additional 7 years following a transplantation versus remaining on dialysis.[6]

Figure 1. Number of Transplants in the US per Year by Age Group[9a]



[a]Data as of March 19, 2018.

Evolution of Solid Organ Transplantation and Immunosuppressive Therapies

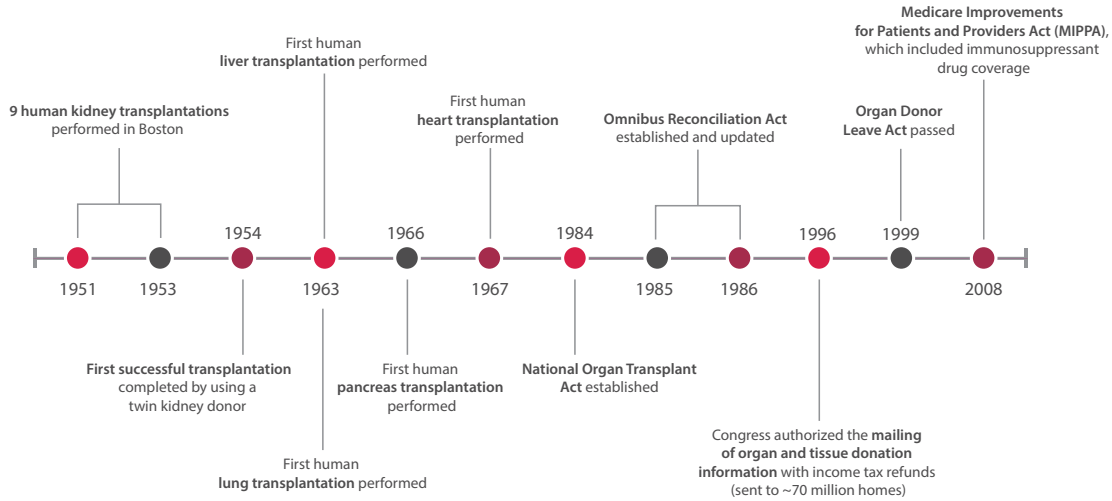
For thousands of years, the desire to replace damaged body parts with live, functioning tissue has existed. However, it was not until the late 20th century that transplantation became a reality due to the advent of immunosuppressive therapies.[1] On December 23, 1954, the first successful solid organ transplantation was completed, bypassing the barrier of rejection by using the patient's identical twin as the kidney donor.[1] This achievement defined a new era for patients with end-stage organ disease and made possible the realization of modern solid organ transplantation.

Early immunosuppressants such as azathioprine[10] in combination with corticosteroids gave new hope to patients with end-stage renal disease by significantly reducing graft rejection rates and improving 2-year kidney transplant survival to 58% at a time when few patients previously survived.[1,11] Transplant survival at the time was largely dependent on having a genetically similar donor, among other factors, yet kidney transplants were more successful in the years following approval of azathioprine than in the period immediately preceding it.[11,12] Nevertheless, azathioprine was associated with substantial toxicities including hepatotoxicity, pancreatitis, anemia, leukopenia, thrombocytopenia, and malignancies.[12] Nearly two decades later in 1983, the Food and Drug Administration (FDA) approval of cyclosporine was instrumental in transforming solid organ transplantation from an experimental option to a viable treatment choice for a majority of patients with end-stage renal disease.[13-15]

ORGAN DONORS

Every 10 minutes, a new individual is added to the national transplant waiting list.[8] Each year, thousands of patients remain on waiting lists for an organ transplantation that can ultimately save their lives.[8] Although patients often remain on waiting lists for years before receiving a transplant, outcomes post-transplantation with proper immunosuppression are mostly positive.[5,8]

Figure 2. Milestones in the Evolution of Solid Organ Transplantation



Immunosuppressant medicines were FDA approved between 1968 and 2011.

As a consequence of the evolution of immunosuppressants, solid organ transplantation now exists as a clinical reality and the standard of care for end-organ disease

During the 1990s with the FDA approval of several immunosuppressant therapies, 1-year graft survival rates among kidney, liver and heart transplants continued to improve[16] such that all (97%) patients receiving a kidney transplant in 2017 will survive the first year.[17] As a consequence of this evolution, solid organ transplantation now exists as a clinical reality.

REGULATORY AND LEGISLATIVE ADVANCEMENTS

Several significant regulatory and legislative advancements have occurred since the first successful transplantation was performed in 1954, all of which contributed to the success of solid organ transplantation. Following FDA approval of early immunosuppressants, the National Organ Transplant Act (NOTA) was enacted to address the nation's organ donation shortage by establishing a registry for organ matching.[3] The Omnibus Reconciliation Act of 1985 and its subsequent 1986 revision further improved patient access to organ donors and transplants by requiring states to have written standards for solid organ transplant coverage in order to qualify for federal subsidy payments. Additionally, it required hospitals to establish policies that allow for family members to donate the organs of a deceased loved one.[2] To further expand the population of organ donors and increase awareness, Congress authorized the mailing of organ and tissue donation information with income tax refunds in 1996. In addition, state legislatures and regulators across the US have passed legislation and implemented programs aimed at improving donor education and easing the pathway to organ donation. For example, several states allow donor registration in conjunction with applying for or renewing a driver's license.

Three years later, in 1999, Congress passed the Organ Donor Leave Act, which allows federal employees to serve as living organ or marrow donors and receive paid leave.[2] In 2008, Congress further advanced transplantations by enacting the Medicare Improvements for Patients and Providers Act (MIPPA), creating guidance that 6 classes of therapies, including immunosuppressants, must be covered under Medicare Part D.

Combined, these actions by Congress have aided in increasing the number of donors and improving access to solid organ transplantation to such an extent that in 2001, the number of living donors exceeded the number of deceased donors in the US for the first time.[2] In 2017, more than 12,000 individuals were listed on the transplant donor list.[21] With one organ donor saving approximately 8 lives, these donors can save nearly 100,000 lives through organ transplantation and successful immunosuppression.[21]

Value of Medicine in Solid Organ Transplantation

Solid organ transplantation with the use of immunosuppressive therapies has become essential to extending life in patients with end-stage organ disease. Without current immunosuppressant drugs, organ transplantation as we know it today would not exist, patient lives could not be extended, and the QOL of patients with end-stage organ disease would not be improved.[17-20]

Table 1. Patient Survival Rates by Type and Years Post-Transplantation[17]

Organ	One-year	Three-year	Five-year
Kidney	97%	93%	86%
Heart	91%	85%	78%
Liver	91%	83%	75%
Lung (single and double)	87%	69%	55%
Pancreas	92%	88%	80%

Rejection Rates

Transplant rejection rates have significantly declined such that patients with end-stage organ disease now have hope of returning to normal health and function after receiving a transplant. Furthermore, adherence to immunosuppressant therapy has consistently demonstrated improved outcomes. Recently, 2-year kidney graft loss rates were reported to be 7.4% in patients with excellent medication adherence compared to 11.5% in patients with poor adherence.[19]

Quality of Life

QOL among patients receiving a kidney transplantation with current immunosuppression drugs has been demonstrated to be virtually "near normal" for the recipient, and in the case of living kidney donation, the kidney donor as well.[20] Studies using the Kidney Disease QOL Short-Form (KDQOL-SF-36) have demonstrated that scores across all domains including general health, physical functioning, physical limitations, pain, emotional well-being, social function, energy/fatigue, and emotional limitations are increased among kidney recipients post-transplant.[20, 22]

Employment

Although employment rates at the time of transplantation are often low, many patients are able to successfully return to work. For example, at the time of a kidney transplantation, employment rates are as low as 23% and 0.6% for patients with private and public insurance respectively; however, only 5% of private insurance patients who were working at the time of transplantation were not employed at 1 year post-transplantation.[23] Although many patients with end-organ disease eventually become too ill to work, many are able to return to their jobs after a successful transplant.[23, 24]

> Almost half (47%) of patients who were working at the time of kidney transplantation have been shown to return to employment within the first year post-transplantation[23]

Costs

From an economic perspective, solid organ transplantation with immunosuppressive therapy has been shown to achieve long-term savings under certain scenarios. Kidney transplantation is the most cost-effective treatment for end-stage organ disease.[5] To illustrate, the cost of one year of life post-kidney transplant is only a fraction of the cost of a life-year on dialysis, which approximates $121,000 annually.[6] While average Medicare reimbursement for kidney transplantation is approximately $83,401 for the first year post-transplantation,[5] after the first year post-transplantation, annual costs associated with a kidney transplant remain stable—around $25,500[5]—which equates to less than one-quarter of the $121,000 total annual cost of dialysis.[5,6] Over the usual course of a lifetime with end-stage kidney disease, when equating costs of dialysis versus costs of a kidney transplant, transplantation can result in as much as $735,000 savings per patient.[6]

Similarly, the average reimbursement for a heart transplant in the first year post-transplantation with Medicare coverage is $298,628[5]; whereas, the cost for a patient with heart failure using a continuous-flow left ventricular assist device is approximately $369,519.[25] This greater than $60,000 in cost savings in the first year post-transplantation is likely attributable to the shorter hospital stays associated with transplantation, fewer readmissions, and more days out of the hospital in comparison to other therapies.[25]

The clinical benefits, cost-savings, life-years gained, and improved overall outcomes associated with solid organ transplantation could not exist without the medicines currently available to control a patient's immune system and prevent organ rejection. As such, immunosuppressive therapies are integral to the success of transplant medicine. While the development of novel immunosuppressants has improved patient outcomes, research in this field is still ongoing. Immunosuppressants have opened doors for newer, cutting-edge approaches to treat end-stage organ disease and paved the way for future research involving regenerative medicine and cell-based therapies that can further improve patient lives.

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