Dimension Integrated Chemistry Systems

Immunosuppressant Drug Monitoring in Transplantation

The solution for consolidating your ISD testing panel

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Transplantation

Transplantation is the act of surgically removing an organ from one person and placing it into another person. Transplantation usually occurs because the recipient's organ has failed or been damaged through illness or injury. While organ transplantation has been performed successfully for years, there is a significant risk in every transplant procedure that the organ will be rejected. The organ (graft) is seen as a foreign substance by the body. Consequently, the immune system is stimulated and attempts to remove the organ from the body. This is known as organ rejection.

Immunosuppressant drugs (ISDs) are prescribed to organ transplant patients to prevent rejection. ISDs suppress the immune response in an attempt to introduce tolerance of the transplanted organ. This prevents organ rejection and improves organ function. Transplant patients typically remain on ISDs for life. Not all ISDs require monitoring, but those with a narrow therapeutic range do. Monitoring ISDs helps to maximize immunosuppression while minimizing the potential toxic side effects that are inherent in ISD therapy.

Transplantation Statistics

The Global Observatory contained information on allogenic donation and transplantation activities for 109 member states, including records of 119,873 solid organ transplants performed in 2014 (+1.8% versus 2013). The most commonly transplanted organ is the kidney (67.8%). Liver transplants also comprise a large percentage of organs transplanted (20.9%). Other organs, such as the heart (5.2%), lungs (3.8%), pancreas (2.11%), and intestines (0.14%), make up a much smaller percentage of the total number of organs transplanted on an annual basis.[1]

Despite increased awareness of organ donation and transplantation, the gap between supply and demand continues to widen. The number of people on the national waiting list continues to grow, while rates of donation and transplant stagnate. On average, someone is added to the transplant waiting list every 10 minutes. On average, 21 people die each day while waiting for a transplant. The number of available organs has stagnated since 2006.

Therapeutic Drug Monitoring of Immunosuppressant Drugs

While each immunosuppressant drug has its own mechanism of action, the utility of ISDs is always aimed at reaching the same goal: to provide adequate immunosuppression so that transplanted organs are not rejected by a recipient's immune system. Clinicians rely on immunosuppressant therapy to help prevent organ rejection. However, they must work carefully to reach an appropriate level of immunosuppression while minimizing the toxic side effects that these drugs have on the patient. Common side effects associated with ISD therapy are nephrotoxicity, neurotoxicity, glucose intolerance, diarrhea, neoplasm, and many others. There are a number of different immunosuppressant drugs available to help support transplant management and classified according to their mechanism of action. Cyclosporine, tacrolimus, mycophenolate mofetil (MMF), everolimus, and sirolimus are currently the most frequently prescribed ISDs.[2]

Calcineurin inhibitors

- **Cyclosporine** is approved for use in heart, liver, and kidney. Therapeutic ranges for cyclosporine are stratified according to transplanted organ, immunosuppressive regimen, induction, and maintenance therapy. The target C0 (Trough concentration, the drug level reached prior to the administration of the drug) is usually 150–300 ng/mL, and, for maintenance therapy, 100–150 ng/mL. In renal-transplant patients, it has been shown that C2 (collected two hours following the administration of the drug) monitoring can be safer than C0. The C2 target is 1700 ng/mL the first month and 800 ng/mL after one year.[3-5]
- **Tacrolimus** is used in liver, kidney, and heart transplants. In 2009, a report from the European Consensus Conference on Optimizing Tacrolimus Therapy in Organ Transplantation was published and provided insight into laboratory practices for monitoring tacrolimus therapy: 12-hour trough sampling (C0) target levels of 5–20 ng/mL.[6] Today, low-dose tacrolimus treatment is becoming the standard of care to minimize Calcineurin Inhibitor (CNI) toxicity. Tacrolimus blood levels are generally maintained in the 4–10 ng/mL range with excellent clinical outcomes.[7]

Antiproliferatives

- **Mycophenolic acid (MPA)*** is used in combination with cyclosporine or tacrolimus in kidney, liver, and heart transplants. Two MPA drugs are available on the market (Mycophenolate Mofetil [MMF] or Mycophenolate Sodium [MPS]), both producing MPA. As a summary, the report of the last consensus conference on TDM of MPA established that, because of a huge variability in the dose-concentration relationship, MPA exposure should be measured and doses should be adjusted accordingly. The area under curve (AUC) is the criterion standard for monitoring because C0 does not correlate well with the AUC due to the multiple types of PK profiles that MPA can exhibit.[8,9] Limited sampling strategies of 20, 60, and 180 minutes after the morning dose have been proposed using the Bayesian estimators to calculate the AUC.[10]

Mechanistic Target of Rapamycin (mTOR)

- **Sirolimus*** is used in combination with other drugs including cyclosporine, tacrolimus, and corticosteroids in kidney transplants only. A consensus guideline for therapeutic drug monitoring of rapamycin was published in 1995.[11] A whole-blood sirolimus therapeutic window of 5–15 ng/mL is recommended for patients at standard risk of rejection, and a target level for sirolimus of 4–10 ng/mL with avoidance in the first two weeks post-transplant is commonly used.[12]
- **Everolimus**† is used in renal-, liver-, and heart-transplant patients along with cyclosporine and steroids and is currently combined with tacrolimus. In transplantation settings, everolimus should be generally targeted to a C0 of 3–8 ng/mL when used in combination with other immunosuppressive drugs calcineurin inhibitors and glucocorticoids); in calcineurin inhibitor-free regimens, the everolimus target C0 range should be 6–10 ng/mL.[13]

The majority of new transplant patients are on low-dose multi-drug regimens and are generally being monitored for all drugs.

With recognized drug testing expertise, Siemens Healthineers offers a comprehensive and expanding menu of tests to meet the ISD testing needs of our customers.

*Product availability will vary from country to country and is subject to local regulatory requirements.
†Not available for sale in the U.S.

Consolidate Your ISD Testing on the Dimension Integrated Chemistry Systems

Patient Care

- Reduces delays resulting from splitting samples
- Offers testing 24 hours/day, 7 days/week
- Provides ISD test results in 20 minutes or less
- Minimizes risk of errors resulting from manual pretreatment
- Validates calibration up to 30 days
- Correlates closely with the LC-MS/MS reference method
- Expands your ISD menu (cyclosporine, tacrolimus, mycophenolate, sirolimus, methotrexate)

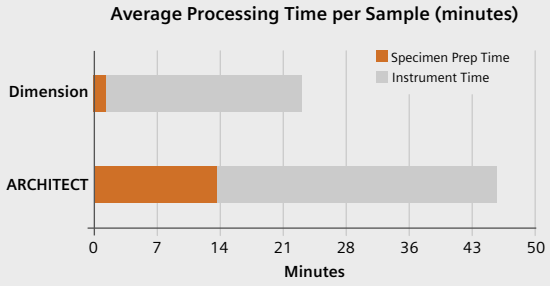
Ease of Use

- Offers continuous loading of samples, reagents, and consumables
- Automates pretreatment of whole-blood samples (CSA/CSE, SIRO and TAC)
- Includes ready-to-use reagents
- Eliminates cuvette carryover from disposable reaction cuvettes
- Lowers system maintenance requirements
- Allows you to perform ISD testing alongside other critical assays

Enhanced Productivity

In a workflow study, ISD testing on the Dimension® Integrated Chemistry Systems reduced manual steps, improved turnaround times, and created a lean laboratory environment.

The Dimension EXL™ systems are considerably faster than the ARCHITECT i2000SR system—three times faster from the start of sample processing (including extraction and pretreatment for the ARCHITECT system) to test result generated by the instrument.[14]



Siemens Healthineers provides a comprehensive menu for ISD testing:

- Cyclosporine/Cyclosporine Extended Range
- Tacrolimus
- Sirolimus
- Mycophenolic Acid

At Siemens Healthineers, our purpose is to enable healthcare providers to increase value by empowering them on their journey toward expanding precision medicine, transforming care delivery, and improving patient experience, all made possible by digitalizing healthcare.

An estimated 5 million patients globally benefit every day from our innovative technologies and services in the areas of diagnostic and therapeutic imaging, laboratory diagnostics, and molecular medicine, as well as digital health and enterprise services.

We are a leading medical technology company with over 120 years of experience and 18,000 patents globally. Through the dedication of more than 50,000 colleagues in 75 countries, we will continue to innovate and shape the future of healthcare.

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

References:

1. GODT 2014. Available from: http://www.transplant-observatory.org/download/report-2014-3/
2. Van Sandwijk, et al. Immunosuppressive drugs after solid organ transplantation. The Journal of Medicine. 2013 Jul/Aug;71(6).
3. Sandimune Cyclosporine Novartis package insert T2015-46. March 2015.
4. Oellerich, et al. Consensus Conference on Cyclosporine. Thera Drug Monit. 1995;17:642-54.
5. Paydas S. Renal Failure. 2005;27:409-13.
6. Wallemacq P. Ther Drug Monit. 2009 Apr;31(2):139-52.
7. Ekberg H. Ther Drug Monit. 2009;31:1-14.
8. Kuypers, et al. Clin J Am Soc Nephrol. 2010;5:341-58.
9. Tett SE. Transplantation Reviews. 2011;25: 47-57.
10. Saint-Marcoux F. Ther Drug Monit. 2011 Jun;33(3).
11. Yatscoff RW. Ther Drug Monit. 1995 Dec;17(6):676-80.
12. MacDonald A, et al. Clin Ther. 2000;22 (Suppl B):B101-B121.
13. Shipkova, et al. Ther Drug Monit. 2016 Apr;38(2).
14. The Dark Daily Report. 2011.

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