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It’s Totally Not the Tacro: Post-Transplant Medication Management Strategies

TODAY’S PANELISTS

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Meet Our Presenter

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Its Totally Not The Tacro?

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Objectives

• Define cognitive impairment

• Outline medication and non-medication related risk factors for cognitive impairment post-transplant

• Describe calcineurin inhibitor (CNI) induced Posterior Reversible Encephalopathy Syndrome (PRES)

• Develop management strategies to address cognitive impairment post-transplant

• Explain the risk of unmanaged cognitive impairment on medical adherence
Cognitive Impairment

- More than 16 million people in the US are living cognitive impairment
- Cognitive impairment:
  - When a person has trouble remembering, concentrating, learning new things, and making decisions that affect their everyday life
  - Can range from mild-severe
    - Mild – see changes however, can still perform daily activities
    - Severe – can lead to losing the ability to understand the meaning or importance of something and the ability to talk or write and then subsequently leads to inability to live independently
Cognitive Impairment in Transplant

• Cognitive impairments lead to decreased self-management capacities and good overall health

• This can lead to medication non-adherence, missing doctors’ appointments, timely communication of medical problems to the healthcare team

Cognitive Impairment in Transplant

- Cognitive impairment is common in patients with kidney disease and affects kidney transplant eligibility and post-transplant outcomes

- Cognitive impairment pre-transplant delays time to listing

- Post-transplant can affect adherence, health care costs, quality of life and graft function

Cognitive Impairment in Transplant

• Up to 87% of patients on hemodialysis and 75% on PD have cognitive impairment

• Kidney transplant can improve cognition, but cognitive impairment is still high post-transplant (22.3-58%)

• Prevalence of dementia is ~17% for kidney recipients aged >75 years compared to 7.5% in the general population

Assessment of Cognition

- Mini mental scale exam (MMSE) one of the most common screens tools utilized
  - Assesses domains of orientation, attention, calculation, recall, language and motor skills
- Montreal Cognitive Assessment (MoCA) is another commonly used test but more sensitive in measuring executive function - this is commonly affected in vascular dementia
  - Gaining popularity in kidney disease
- If screening is positive for cognitive impairment a thorough evaluation with additional neuropsychological tests should be completed

Pathophysiology of Cognitive Impairment

• Pre-transplant
  • Association between uremia and cognitive impairment is well known
  • Brain and kidney have common vascular characteristics
    • Low vascular resistance and receive high blood flow and have similar vasoregulatory system
    • With small disease in one organ could be a sign of disease in another one
  • CKD and dementia have common risk factors
    • HTN, hyperlipidemia, obesity, DM, metabolic syndrome, and smoking

Pathophysiology of Cognitive Impairment

• Structural brain changes in CKD
  • White matter changes
    • ESRD is associated with increased white matter disease, clinical and subclinical strokes and cerebral atrophy
  • Alterations in cerebral blood flow
    • ESRD associated with increased in cerebral blood flow
    • Cerebral blood flow decreases after transplant
    • CNIs may play a role due to their vasoactive properties
  • Alterations in brain metabolites
    • ESRD associated with alterations in brain metabolites
    • Ratio of choline/creatinine are increased in ESRD and this can affect changes in osmotic pressure

Pathophysiology of Cognitive Impairment

- Perioperative factors
  - Post-transplant delirium is associated with subsequent diagnosis of dementia
  - CNIs in the brain inhibit calcineurin inhibiting calcineurin resulting in altered neurotransmission, calcium homeostasis and gene expression, therefore, impairing response ischemic injury and affecting cognition
  - CNIs can also lead to posterior reversible encephalopathy syndrome (PRES)

Goals of Immunosuppression

• Induction
  • Prevent ischemia reperfusion injury
  • Prevent early rejection

• Maintenance Immunosuppression
  • Less-potent agents used for long-term immunosuppression post-transplant
  • Prevent acute and chronic rejection
  • Minimize medication-related adverse effects

• Combination therapy involving multiple medications
  • Maximization of immunosuppression
  • Minimization of adverse effects
  • Flexibility of rapid adjustments
  • Effective coverage of immune system “redundancy”

Calcineurin Inhibitors (CNI)

**Tacrolimus**
- Binds to FK binding protein 12 (FKBP12) within the cytoplasm of T cells
- Forms tacrolimus-FKBP12 complex
  - Inhibits phosphatase activity of calcineurin
- Calcineurin can no longer dephosphorylate nuclear factor of activated T cells (NFAT), that when dephosphorylated activates mRNA transcription of IL-2
- Therefore, inhibits the production of IL-2 and reduces the activation of cytotoxic T lymphocytes

**Cyclosporine**
- Binds to cyclophilin within the cytoplasm of T cells
- Cyclosporine-cyclophilin complex:
  - Inhibits the phosphatase activity of calcineurin
- Calcineurin can no longer dephosphorylate NFAT, that when dephosphorylated activates mRNA transcription of IL-2
- Therefore, reduces transcription of IL-2 and reduces early activation of cytotoxic T lymphocytes

Tacrolimus PK

- Very large intra and inter patient variability
- Very lipophilic, binds with higher affinity to RBCs, therefore blood concentration is greater than serum concentration
- If levels are measured by MEIA then they may appear artificially high in the setting of low hematocrit and low albumin
- Bioavailability following PO intake is ~25%
  - Lower when administered with low fat foods
  - Higher in the setting of diarrhea
  - Independent of bile

Adverse Effects

Cyclosporine > tacrolimus
- Hypertension, hyperlipidemia, hirsutism, gingival hyperplasia

Common in both
- Nephrotoxicity, hyperkalemia, magnesium wasting, neoplasms, infection

Tacrolimus > cyclosporine
- Hyperglycemia, alopecia, neurotoxicity, PRES

Effects of Diarrhea on Tacrolimus

Tacrolimus is absorbed in the duodenum and the jejunum. Shorter duration of ileal time may result in more tacrolimus delivery to the colon and therefore more absorption. Sloughing of intestinal lining due to diarrhea may disrupt P-gp recycling into the intestinal lumen.

Drug Interactions

P-gp = potential inhibitor (conflicting data)
CYP3A4 = SUBSTRATE

QT prolongation
Hyperkalemia

Statins - thought to increase the clearance of cyclosporine due to affinity for lipoproteins, though this was not statistically significant in studies.

Diltiazem - enzyme inhibition, reduce cyclosporine dose 20%
Azoles - enzyme inhibition, increased absorption by Pgp in intestinal mucosa, reduce dose 75%
Additive QT prolongation
Antacids - limit absorption
Once Daily Options

- Utilization of once daily tacrolimus – Envarsus
  - Melt dose technology
  - Slow release of the drug
  - Less neurologic toxicity
  - Avoid the peaks that occur with immediate release tacrolimus

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES first described in 1996
The incidence of PRES after transplant is about 0.5-5%
Etiology multifactorial
  › Hypertensive encephalopathy
  › Eclampsia
  › Immunosuppressive drugs
  › Autoimmune diseases

PRES

Risk Factors

› Hypomagnesemia
› Hypercholesterolemia
› Vasoactive agents
› Erythropoietin
› Blood transfusion
› Antineoplastic drugs
› Peritoneal dialysis
› Immunosuppressive drugs - CNI

PRES

Clinical Features

› Seizures
› Acute encephalopathy syndrome
  › Confusion, headache, vomiting, altered consciousness, mental status changes
› Visual symptoms
  › Hemianopsia, loss of visual acuity, visual blurring, blindness, diplopia

Time course

› Varies

Diagnosis/Imaging

› MRI
  › Abnormal and reversible increased signal on FLAIR images
› Angiography
  › Reveal focal or diffuse vasoconstriction, vasodilation appearance

Mechanism of PRES

› Hyperperfusion – severe hypertension leads to transient impairment of autoregulation that causes cerebral vasodilation and vasogenic cerebral edema

› Hypoperfusion – neurotoxicity and offending agents and hypertension lead to autoregulatory vasoconstriction leading to hypoperfusion, ischemia and edema

PRES

Management post transplant
› Reversible when offending agent has been stopped
› Permanent neurological deficits and cerebral infarcts may appear because of late recognition

CNI’s major risk factor
› Hold offending agent and utilize an alternative agent

Symptom treatment
› Seizures – needs to be controlled immediately
› Blood pressure

Cognitive Impairment and Non-Adherence

• Medication adherence is defined as patient’s ability to follow recommended treatment plans

• Up to 1/3 of solid organ transplant recipients have non-adherence to immunosuppression during the 1st year of transplant leading up to 36% of kidney allograft losses

• At 3 years post-transplant, non-adherence can cost up to $33,000 per patients

• Non-adherence leads to 125,000 deaths per year and 33-69% of hospital admissions are related to non-adherence

Cognitive Impairment and Non-Adherence

- Risk factors for non-adherence
  - Age
  - Education and income levels
  - Requirements of treatment
  - Adverse effects of immunosuppressants
  - Time since transplantation

The Association between Psychosocial and Age-Related Factors with Adherence to Immunosuppressive Therapies after Renal Transplantation

• Cross-sectional study in kidney transplant recipients
• Adherence was assessed with Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS)
• Psychosocial and age related variables were measured with World Health Organizations Quality of Life questionnaire
• Linear regression:
  • Significant predictors of self-reported adherence (P <0.05) were age, time since transplant, anxiety and cognitive functions

How Strategies to Improve Adherence

• Mobile Health
  • Technology has been found to be an effective way to educate people on a number of topics
  • Converting paper education to video education has significantly increased knowledge about various topics
  • McGillicuddy et al and Browning et al established prevalence data that matched national estimates, with kidney transplant recipients usage of smart phones has increased from 35% to 61%
    • 78% are willing to incorporate mobile health into their care

Post-transplant adherence remains one of the most important factors for long term graft and patient survival.

Mobile health might be able to affect the at-risk population.

Various strategies have been utilized:

Significant increase in adherence to labs monitoring in 33 liver transplant recipients after utilizing text message reminders over a 1-year period (78% vs 58%, p<0.001) while the no intervention group showed no change (57% vs 61%, p=0.38).

How Strategies to Improve Adherence

- Other strategies include electronic medication tray, bluetooth enabled blood pressure monitors, and smartphone for usual care.
- McGillicuddy et al. compared patients receiving an mHealth intervention including:
  - Wireless electronic medication tray with timestamping
  - Bluetooth enabled blood pressure monitor
  - Smartphone for usual care
    - Included 20 transplant patients with <85% adherence to medication

How Strategies to Improve Adherence

- Patients were reminded at regular intervals to measure blood pressure and they were contacted for nonadherence
  - If measurements were outside of range than the coordinator was alerted
  - Providers received a weekly report
  - During the 3–month intervention where was a 91% retention rate and both adherence and blood pressure significantly improved in the mHealth group
- Long term effects were assessed as well and the intervention group continued to exhibit lower SBP than patients in the control group 12 months after the trial ended

Summing It All Up

• Cognitive impairment is a trend seen in solid organ transplant
• Standard of care medications used for solid organ transplant such as CNIs can cause cognitive impairment
• Cognitive impairment can lead to medication non adherence leading to poor graft function
• Strategies to improve adherence:
  • Pill boxes
  • Electronic pill boxes
  • Text message reminders
  • Alarm clock reminders
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A Special Thanks to Our Presenter

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