


Pharmacology: Five New Transplant Medications

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Objectives

- Describe five new transplant medications
- Review the mechanism of action, currently known adverse events, and potential place in therapy for new agents
- Review of the available literature




New Agents

- Small molecules
 - ISA247
 - AEB071
- Biologic Agents
 - Belatacept
- Anti-Adhesion Agents
 - Alefacept
 - Efalizumab
- B-Cell Agents
 - Bortezomib



How does a drug make it to market?




Trial Overview

- **Pre-Clinical**
 - Pre-clinical studies involve in vitro and in vivo experiments to evaluate the study drug for efficacy, toxicity, and pharmacokinetic properties
 - Decide if there is scientific value for further development as new drug
- **Phase 0**
 - Human microdosing study
 - No efficacy or safety data




Trial Overview, cont.

- **Phase 1**
 - First stage of testing in human subjects
 - Small group of **healthy** volunteers (n=20-50)
 - Assesses safety, tolerability, pharmacokinetics, and pharmacodynamics
- **Phase 2**
 - Performed on larger groups (n= 20-300)
 - Assess continued efficacy and safety




Trial Overview, cont.

- **Phase 3**
 - Phase III studies are randomized controlled multicenter
 - Patient groups (n=300–3,000)
 - Definitive assessment of how effective the drug is
 - Compare with current 'gold standard' treatment
- **Phase 4**
 - Post-marketing Drug Surveillance




Small Molecules

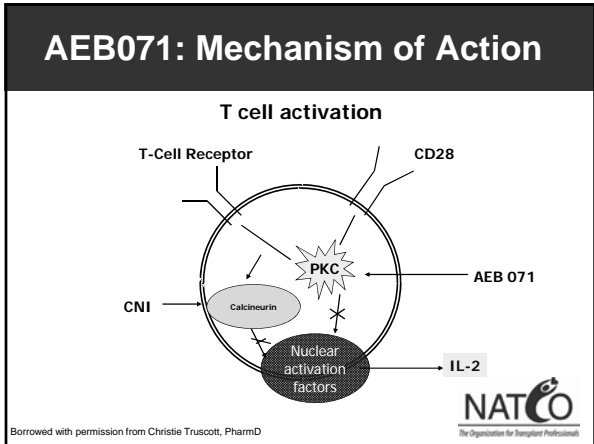
AEB071



AEB071 (Sotrastaurin)

- **Oral agent**
- **Novel class of medication**
 - Protein Kinase C (PKC) Inhibitor
- **Mechanism of Action**
 - Prevention of T-cell activation and IL-2 secretion





- ### AEB071: The Potential Role
- **Prophylaxis of organ rejection**
 - A possible replacement therapy for calcineurin inhibitors (CNI)
 - Newer evidence suggest may be more suited as an adjunct to CNIs
 - **Phase 1 and moving into Phase 2 trials**
- NATCO**
The Organization for Transplant Professionals

- ### Phase I Trial
- **Administered as single or multiple doses for up to 2 weeks**
 - Favorable pharmacokinetic (PK) profile
 - Well tolerated
 - **Multiple dose study** (Slade et al 2006)
 - Double blinded, placebo controlled, ascending dose method
 - N=24 (n=6/group)
 - Doses 25, 100, 200 mg or placebo twice daily x 2 weeks
 - All doses well tolerated
 - Linear PK for all doses
 - AUC was dose-proportional
 - Trough levels used as surrogate to AUC
- NATCO**
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Phase 2 Trials

- **Two trials were stopped for an increased rate of rejection**
 - **First Trial:** CNI avoidance with higher rates of rejections noted versus the control group (FK/MPA)
 - **Second Trial:** CNI withdrawal at 3 months and switched to MPA and AEB based therapy
- **European trial is ongoing**
 - Comparing combination therapy with AEB071, Everolimus, steroids vs. FK, MPA, and steroids

Friman S et al. Presented at ATC 2009.
Vincenz F, Kirk AD. *Ann J of Transplant* 2008



Small Molecules

ISA247



ISA_{TX} 247


- **Novel calcineurin inhibitor**
 - New evidence indicates CNI toxicity due to depletion of high-energy phosphate intermediates in mitochondria
 - Semi-synthetic analog of CyA
 - Generic name: Voclosporin
- **Phase I in vitro studies**
 - Suggest ~3x as potent as cyclosporine
- **Decreased toxicity profile**

Abel M, et al. J Heart Lung Transplant; 2001
Snijder M, et al. J Heart Lung Transplant 2003; 22:1341-1352



ISA_{TX} 247: The Potential Role


- **Replacement of traditional Calcineurin Inhibitors**
 - More potent with less nephrotoxicity?
 - Use in combination with induction, MMF/MPA and steroids??

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Pre-Clinical Data

- **In vitro study**
 - Immunosuppressive activity measured by calcineurin assay
- **In vivo study**
 - Immunosuppressive efficacy studies performed in rat heart transplant models
- **Toxicity study**
 - Performed in rats, rabbits, and dogs


Abel M, et al, J Heart Lung Transplant, 2001

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Pre-Clinical Data

- **Results**
 - Mean survival time for ISA treated animals was 56.5 days vs. 18.2 days for CyA treated animals
 - >80% of animals rejected with CyA
 - 20% of animals rejected with ISA equipotent dosing
 - Good oral absorption, BID dosing


Abel M, et al, J Heart Lung Transplant 2001

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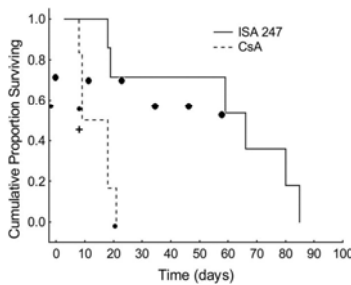
ISA247 Significantly Prolongs Renal-Allograft Survival in Nonhuman Primates

- **Objective**
 - Compare survival times of renal allografts in nonhuman primates treated w/ ISA vs. CyA
- **Methods**
 - Renal tx preformed on male monkeys
 - CyA 15 mg/kg q 12 hr (n= 7) *OR*
 - ISA247 75 mg/kg q 12 hr (n=8)
 - Dose adjusted to maintain blood level of 150ng/mL

Gregory CR, et al. Transplantation 2004;78:681-685




ISA247 Significantly Prolongs Renal-Allograft Survival in Nonhuman Primates



• Monkeys survived significantly longer in the ISA group (p=0.0036)

- ISA mean survival time 50.43 ± 28.93 days
- CyA mean survival time 13.83 ± 5.78 days


Gregory CR, et al. Transplantation 2004;78:681-685



ISA247 Significantly Prolongs Renal-Allograft Survival in Nonhuman Primates

- **Adverse events**
 - Severe, non-regenerative anemia in 50% of monkeys treated with ISA
 - Simian parvovirus?
 - PTLD development in 3 of the ISA treated monkeys
 - More potent CN inhibition?
 - Primate gamma-herpes virus?


Gregory CR, et al. Transplantation 2004;78:681-685



Phase II Trial

- **ISA247 vs. Tacrolimus in renal transplant recipients (N=334)**
 - Three dose ranges for ISA
 - 0.4mg/kg
 - 0.6mg/kg
 - 0.8mg/kg
 - Induction with IL-2R antagonist, MMF, and steroids


Vinceri F, Kirk AD, Am J of Transplant 2008; 8:1972-81



Phase II Trial


- **Preliminary Results**
 - Rejection rates low in all groups
 - **ISA:** 10.7%, 9.1%, and 2.3% (by dose range)
 - **Tacro:** 5.8%
 - Renal function similar b/w all groups
 - Post transplant diabetes
 - Noted to be less frequent in ISA groups
- **With these favorable results, ISA should move onto Phase III trials**

Vinceri F, Kirk AD, Am J of Transplant 2008; 8:1972-81




Biologics

Belatacept (LEA29Y)




Belatacept (LEA29Y)

- **Derived from abatacept**
 - Human fusion protein combining the extracellular portion of cytotoxic T lymphocyte-associated antigen 4 (CTLA4) with the constant fragment of human IgG1 (CTLA4Ig)
 - Treatment for T- cell mediated autoimmune disorders (RA, Psoriasis)
- **Selective co-stimulation blocker**
 - Belatacept is 2 amino acids different from abatacept
 - Binds surface co-stimulatory ligands (CD80 and CD86) of antigen presenting cell (APC)
 - Blocks T cell activation and promotes cell death
- **Route of Administration**
 - Given IV over 30 minutes



Belatacept: The Potential Role


- **Replacement for calcineurin inhibitors**
 - Possibly avoid the renal toxicity associated with CNIs with the same efficacy??



Clinical Development Overview

- **Phase I (IM103-001)**
 - Randomized, Double Blind, Placebo Controlled Study to Assess the Pharmacokinetics, Immunogenicity, and Safety of Escalating Doses of BMS-188667 Given as a Single Intravenous Infusion to Patients With Psoriasis Vulgaris
 - Single ascending dose study (0.1 – 20 mg/kg)
 - N = 40 (Belatacept - 30; Placebo – 10)
 - T_{1/2} = 8-9 days
- **Phase II**
 - IM103-002: 6 month efficacy and safety in subjects with RA
 - N=214 (Belatacept - 92; CTLA4Ig – 90; Placebo – 10)
 - IM103-100: Renal transplant study
 - N=218 (Belatacept – 145; CsA -73)

Vincenzi F, Larsen C, Durrbach A, et al. *N Engl J Med* 2006; 353: 770-81



IM103-100 Primary Study Objective

- “To demonstrate that belatacept was not inferior to cyclosporine in its ability to prevent acute rejection at six months”

IM103-100 Study Design

- “Patients who had had one episode of rejection by month 6 were considered to have reached the primary end point”

Vincenti F, Larsen C, Durrbach A, et al. *N Engl J Med* 2005; 353: 770-81.



IM103-100 Study Design

- **Patients assigned to 3 groups (N=218)**
 - Intensive Belatacept (N= 74)
 - Less-intensive Belatacept (N=71)
 - Cyclosporine (N= 73)
- **Induction/ Immunosuppression**
 - All pts received Basiliximab 20mg (POD #0, 4)
 - MMF 1000mg twice daily
 - Steroid taper (minimum of Prednisone 5mg daily)

Vincenti F, Larsen C, Durrbach A, et al. *N Engl J Med* 2005; 353: 770-81



IM103-100 Study Results

- **Incidence of acute rejection at 6 months was comparable among the 3 groups**
 - Non-inferiority shown with CyA for ACR
- **No episode of rejection noted after 6 months in any group**
- **GFR rate at 1 year was higher in both belatacept groups vs. CyA group (P=0.01)**

Vincenti F, Larsen C, Durrbach A, et al. *N Engl J Med* 2005; 353: 770-81



IM103-100 Study Results

- **Both dose regimens appear acceptable for Phase III**
 - **Similar/ favorable trends as compared to CyA for:**
 - **Patient/Graft Survival**
 - 1 pt died in belatacept arm vs. 4 in Cya
 - **Observed rate of rejection**
 - Belatacept 6-7% vs. CyA 8-17%
 - **Chronic Allograft nephropathy**
 - Intensive Belata 29% vs. Less Intensive Belata 20%, vs. CyA 44%

Vincenti F, Larsen C, Durrbach A, et al. *N Engl J Med* 2005; 353: 770-81



IM103-100 Conclusions

- **In comparison to CyA, Belatacept treated patients appear to have:**
 - **Comparable patient/graft survival and ACR**
 - **Favorable GFR, renal histology at 1 year**
 - **Comparable safety overall, with modestly more favorable cardiovascular/metabolic changes**

Vincenti F, Larsen C, Durrbach A, et al. *N Engl J Med* 2005; 353: 770-81



Phase III Study


- **Randomized, Phase III Study of Belatacept vs CyA in Kidney Transplant Recipients (BENEFIT)**
 - **Adults with living or DD renal transplant**
 - **Randomized to 3 groups (n = 666)**
 - **More intensive (MI) 10mg/kg x 6 months, then 5mg/kg x 4 wks**
 - **Less intensive (LI) 10mg/kg x 4 months then 5mg/kg x 4 wks**
 - **CyA 150-300ng/mL until month 1, then 150-250 ng/mL**
 - **De novo recipient: PRA < 30% or**
 - **Retransplant: PRA < 30%**
 - **Induction: Basiliximab, MMF, steroid taper**

Vincenti F, et al. Presented at ATC, 2009




BENEFIT -- Outcomes

- Patient and Graft Survival similar
- Percent of pts with CAN at 1 yr was similar
- Infection rates similar
 - ? More PTLD in Belatacept groups?
 - 3 pts in MI group, 2 in LI group, 1 in CyA
- ****Results/ manuscript are in process**



Phase III Study


- **Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial - Extended Criteria Donors (BENEFIT-EXT)**
 - Decreased donor meeting extended criteria donor (ECD)
 - Randomized to 3 groups (n= 543)
 - More intensive (MI), Less intensive (LI), or CyA
 - De novo renal transplants
 - PRA < 30%



Durrbach A, et al. Presented at ATC 2009. Abstract #27

BENEFIT EXT -- Outcomes


- Patient and Graft Survival similar
- Percent of pts with CAN at 1 yr was similar
- Infection rates similar
 - ? More PTLD in Belatacept groups?
 - 2 pts in MI group, 3 in LI group, 0 in CyA
- ****Results/ manuscript are in process**



Anti-Adhesion Molecules

Alefacept (Amevive®)

Efalizumab (Raptiva®)




Alefacept

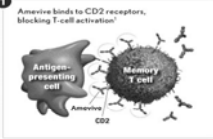
- **Currently available as Amevive®**
 - Treatment for plaque psoriasis
 - Approved in 2003
 - 15 mg/ 0.5 mls IM or 7.5 mg/ 0.5 mls IV

Recommended dosing regimen

12 weekly treatments	Treatment break ≥12 weeks	12 weekly treatments	Treatment break ≥12 weeks
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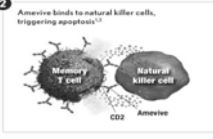


Alefacept: Mechanism of Action




1 Alefacept binds to CD2 receptors, blocking T-cell activation¹¹

- **Lymphocyte function-associated antigen-3-IgG (LFA-3-IgG) fusion protein**
 - Targets T-cells by selectively binding to the lymphocyte antigen CD2 and inhibiting any LFA-3 and CD2 interaction
 - Prevents T cell activation
 - Reduces subsets of CD2 lymphocytes by bridging them to immunoglobulin receptors on cytotoxic cells (natural killer cells) and leads to apoptosis of memory T cells



2 Alefacept binds to natural killer cells, triggering apoptosis¹²



Alefacept: The Potential Role

- **Target costimulation blockade (CoB) resistance cells**
 - Heterologous alloreactive T- Cell memory
- **GVHD**
- **Organ Transplantation??**



Rapid response to alefacept in patients with steroid resistant or steroid dependent acute GVHD

- **Prospective, N = 7 (8 episodes)**
- **Primary Objective**
 - Evaluate the effect of alefacept in steroid resistant/dependent acute GVHD
- **Inclusion criteria:**
 - **Grade 2 - 4 acute GVHD**
 - Steroid resistant – progression after 3 days standard treatment; unresponsive to 7 days standard therapy
 - Steroid dependent – responds to MP 2mg/kg/day but relapsing with an attempt to decrease
- **Standard Therapy**
 - Cyclosporine 3mg/kg/day
 - MP or equivalent CS \geq 2mg/kg/day



Sharira MY et al. Rapid response to alefacept given to patients with steroid resistant or steroid dependent acute graft-versus-host disease: a preliminary report. Bone marrow Transplantation (2005) 36, 1091-1101.

Rapid response to alefacept given to patients with steroid resistant or steroid dependent acute GVHD


- **All patients responded**
 - One patient with skin and two with GI involvement whom had an early partial response developed exacerbation and CR was not achieved
- **Rapid response can be seen within days**
 - Rapid response especially with skin involvement
- **No immediate side effects were observed**
 - Increased infection rates?
- **Pediatric patient with grade 4 GVHD**
 - Responded quickly
 - Exacerbation seen after 5 days -- Dose repeated & responded
 - All pediatric changed to 15mg/dose x 2 /week
 - May offer significant non-harmful intervention



Sharira MY et al. BMT; 2005 36, 1097-1101.

Alefacept Conclusions


- **Further studies need to be done to determine use in transplantation**
 - Phase II trials in kidney transplant underway
 - Multicenter trial to assess safety and efficacy



Anti-Adhesion Molecules


Alefacept (Amevive®)

Efalizumab (Raptiva®)




Efalizumab

- **Brand name -- Raptiva®**
 - Treatment for plaque psoriasis
 - Approved in 2003
 - **Voluntarily pulled from the market in the United States**
 - Increased risk of PML (Progressive Multifocal Leukoencephalopathy)
 - **Unable to determine who was at risk of developing PML**




B-Cell Agent

Bortezomib (Velcade)



Bortezomib


- **Currently available as Velcade®**
 - Approved for multiple myeloma in 2005
 - Dosed at 1.3 mg/m² (Myeloma dosing)
 - Given as a 3-5 second bolus



Velcade (bortezomib); Package Insert

Bortezomib: Mechanism of Action

- **Antibody Mediated Rejection (AMR)**
 - **Proteasome inhibitor**
 - Targets 26s proteasome complex
 - Processes/degrades excess proteins in active plasma cells
 - **Inhibition of IL-6 production by bone marrow stromal cells**
 - Apoptosis in different phases of B-cell maturation
- **Acute Cellular Rejection (ACR)**
 - Apoptosis induction in activated T-cells, T-cell depletion, NF-κB inhibition



Everly M.J. Transplantation 2008; 86:1754-1761

The Potential Role of Bortezomib

- **Treatment of Antibody Mediated Rejection**
 - Also noted efficacy in the treatment of Acute Cellular Rejection
- **Preliminary success as a last line agent**
- **More trials needed to determine its use sooner in rejection therapy**

Everyly MJ, Transplantation 2008; 86:1754-1761



Adverse Effects

- **Cardiovascular**
 - Edema (11% to 28%)
 - Hypotension (12% to 15%)
- **Central nervous system**
 - Fever (19% to 37%)
- **Dermatologic**
 - Rash (17% to 28%)
- **Gastrointestinal**
 - Diarrhea (47% to 57%), Constipation (40% to 50%), Anorexia (34% to 39%), Nausea (44% to 57%), Vomiting (27% to 35%)
- **Hematologic**
 - Thrombocytopenia (21% to 38%)
 - Anemia (17% to 30%)
 - Neutropenia (6% to 19%)
- **Neuromuscular & skeletal**
 - Weakness (61% to 72%)
 - Peripheral neuropathy (36% to 55%)

Velscade (bortezomib): Package Insert



Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection

- **The Cincinnati experience**
 - Clinical evidence for the use of bortezomib in AMR therapy
 - Used bortezomib 6 pts with AMR + ACR
 - Refractory to plasmapheresis ± IVIG± ATG± rituximab therapy

Everyly MJ, Transplantation 2008; 86:1754-1761



Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection

• Results

- All allografts were salvaged w/out any documented opportunistic infections
- Resolution of refractory ACR
- Sustained decrease in DSA in all patients
 - Within 2-4 weeks of receiving bortezomib
- Authors did note some rebound DSA



Everly MJ. Transplantation 2008; 86:1754-1761

Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection

• Results/ Conclusions

- Rebound DSA may be combated by multiple cycles for more sustained decrease in DSA?
 - Multiple myeloma treatment is twice weekly on days 1, 4, 8, 11, 22, 25, 29, and 32
 - Then given once weekly for another 6 weeks
 - 10 day rest period in b/w cycles




Stay Tuned for Other Therapies on the Horizon...



Others

- **JAK-3**
 - Increased infection rates w/ higher dose, moving through clinical trials
- **Epratuzumab**
 - CD22 specific monoclonal antibody
 - Targets memory B-cells or those responsible for antibody formation
- **4D11**
 - CD40 specific antibody
 - Prophylaxis of rejection
- **Natalizumab**
 - Anti-integrin monoclonal ab (approved for MS/ Crohn's disease)
 - Pulled from the market for PML, now re-emerging for tx
- **Eculizumab**
 - C5a specific monoclonal ab
 - Antibody mediated rejection?


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