Curricular Track I—The Role of the Immune System in Disease Pathophysiology: Implications for Pharmacotherapy
Activity No. 0217-0000-11-066-L01-P (Knowledge-Based Activity)

Monday, October 17
9:15 a.m.–10:45 a.m.
Convention Center: Spirit of Pittsburgh Ballroom A

Moderator: Tien M.H. Ng, Pharm.D., FCCP, BCPS
Associate Professor, Department of Pharmacy Practice, University of Southern California, Los Angeles, California

Agenda

9:15 a.m.  Overview of the Immune System and Application to Disease Pathophysiology
Val R. Adams, Pharm.D., FCCP, BCOP
Associate Professor of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Lexington, Kentucky

9:45 a.m.  Immunotherapy in Neurologic Disease
Melody Ryan, Pharm.D., MPH, FCCP, BCPS, CGP
Associate Professor, University of Kentucky, Lexington, Kentucky

10:15 a.m.  PRO/CON Debate: Targeting Inflammation and the Prevention and Treatment of Cardiovascular Disease
Sheila L. Stadler, Pharm.D., BCPS (AQ Cardiology)
Clinical Pharmacy Specialist, Kaiser Permanente of Colorado, Aurora, Colorado; Clinical Assistant Professor, University of Colorado–Denver School of Pharmacy, Aurora, Colorado

and

Craig D. Williams, Pharm.D.
Clinical Associate Professor, Department of Pharmacy Practice College of Pharmacy, Oregon Health & Science University, Portland, Oregon

Faculty Conflict of Interest Disclosures

Val R. Adams: no conflicts to disclose
Melody Ryan: no conflicts to disclose
Sheila L. Stadler: no conflicts to disclose
Craig D. Williams: no conflicts to disclose
Learning Objectives

1. Describe the key components of the innate immune system and acquired immune response.
2. Identify how components of the immune system can contribute to pathophysiologic processes of disease.
3. Describe the current understanding of the pathophysiologic mechanisms of immune-mediated neurologic disease.
4. Evaluate the evidence and controversies for the use of immunomodulating therapy in the treatment of demyelinating neuropathies.
5. Discuss the evidence for inflammatory markers and their association with various cardiovascular diseases.
6. Compare and contrast the evidence for treatment modalities targeting inflammation and their effect on clinical outcomes.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Overview of the Immune System and Application to Disease Pathophysiology

The Immune System
An Army Within
- A crucial component for survival
- Well coordinated system primarily focused on killing foreign invading predators (but it does much more)
- If it becomes dysfunctional due to communication errors, lack of soldiers, etc. the risk of damaging the nation goes up drastically
- An overview of the ranks, their charges, and communications, and will be reviewed.

Immune System
- Protection against pathogens
- Allergic reactions to innocuous substances
- Organ graft rejection
- Autoimmunity
- Tumor immunity/surveillance
- Others
  - Atherosclerosis
  - Neuronal protection
  - Angiogenesis
  - Lipid metabolism

Pathogen Response

Objectives
1. Describe the key components of the innate immune system and acquired immune response.
2. Identify how components of the immune system can contribute to pathophysiologic processes of disease.

Conflicts of Interest
I have no real or perceived conflict of interest to report
Innate Immunity: Soldier on Patrol (Phagocytes)

- **Macrophages**
  - First on the scene, resident in most tissues (skin, mucosal surfaces, vessels)
  - Recognize bacteria, fungus, virus via receptor(s) that recognize common pathogen surface constituents (activate the macrophage)
  - Pathogen is engulfed and degraded
  - Communication to comrades via cytokines/chemokines
  - Recruitment of other cells (neutrophils) and initiation of inflammation

Innate Immunity: MØ Recognize Patterns

**Scavenger:** e.g. SR-A or CD36

**GPI-anchored:** e.g. CD14

**Integrin** e.g. CR3 (CD18/11b)

**Toll-like receptors** e.g. TLR2, TLR4

**Ig Superfamily:** e.g. FcR

Innate Immunity: MØ Activation Response

- Activated MØ engulfs pathogen and secretes cytokines/chemokines

- TNF-α – Vascular effects, permeability allowing cell, Ig, complement access, ↑ lymph drainage, fever, shock

- IL-1 – Vascular effect, activates Lymphs, local tissue destruction, fever, 1↑IL-6

- IL-6 – Lymph activation, ↑ Ig production, fever, acute phase protein production

- IL-8 (CXCL8) – Chemotactic factor to attract neutrophils, basophils, and T-cells to site

- IL-12 – Activates NK cells, induces differentiation of CD4 cells to Th1

Innate Immunity: Complement

**Classical Activation**
- Antigen: Antibody
- Activation of the Complement Cascade
- C3a, C5a
  - Inflammatory mediator
  - Recruitment of phagocytes
- C3b (opsonization)
  - binds to complement receptors on phagocytes – leads to removal of pathogens

**Lectin Activation**
- Lectin binding to Pathogen surface
- C3b (opsonization)
  - Binds to complement receptors on phagocytes – leads to removal of pathogens

**Alternative Activation**
- Complement binding to pathogen surface
- Formation of a membrane attack complex (MAC)
  - Creates holes in cell wall leading to death.

Innate Immunity: Next to Arrive: Neutrophils

- Neutrophils (inflammatory cell responder)
  - Attracted to the infection via chemokines (e.g., IL-8)
  - Vascular effects (part of inflammation): vasodilation (slow blood flow), increased endothelial adhesion and molecule expression; allowing neutrophils to adhere to the vessel at the infection site, then exit the circulation into the tissue (diapedesis), where they can identify pathogens via receptors (similar to MØ) and phagocytize and destroy them.
  - Short lived and usually die after phagocytosis

Inflammatory Response

- Normal Vessel w/ Neutrophil
- Inflamed vessel w/ Neutrophil

Janeway's Immunobiology 7th ed Garland Science
Innate Immunity: Natural Killer Cells

- Lymphoid cells that circulate in blood and are activated by IL-12 and IFN-α and IFN-β
- IL-12 synergistically with TNF-α stimulate NK cells to make and secrete INF-γ
- Recognize cells through (activating & inhibiting) surface receptors to help differentiate normal cells versus abnormal/infected target cells
- Release cytotoxic granules that kill target cells

Innate Immunity: Inflammation

- Cytokines release initiated by MØ – then expanded
- Lipid inflammatory mediators: prostaglandins, leukotrienes, and platelet-activating factor are enzymatically produced by MØ
- 3 essential roles
  - Augment killing by front line cells
  - Induce local blood clotting to prevent infectious spread to the blood
  - Promote tissue repair and healing

Inflammatory Response

- Activated monocytes differentiate into MØs and dendritic cells and can become antigen presenting cells (APCs), which bridge the innate and adaptive Immune system

Antigen Presentation

- Professional APCs
  - Macrophages, dendritic cells, B cells
  - Present antigens in context of MHC molecules
  - MHC – I: presents to CD8+ T cells
    - Expressed on all nucleated cells
    - Present antigens from intracellular pathogens (virus)
  - MHCII—presents to CD4+ T cells
    - Expressed mostly by lymphoid cells (APCs)
    - Present antigens from extracellular pathogens (Bacteria)

Cell Mediated Immunity

All about the T-cell

- Stimulates MØ Prod. IL-2, INF-γ
- Stimulate B-cell (IL-4, IL-6) differentiation to plasma cells
- Not pictured: T reg which suppress The immune system (IL-10)
T-cell activation/inhibition

```
Ag + Antigen; CD28: CD80/CD86-associated antigen 1; T = T-cell; MHC = major histocompatibility
```

T-cell signal transduction

```
APC
CD4/CD8
CD3
T cell
Ca++ dependent
DAG
PKC path
RAS, ERK
JNK path
NFAT
NF-κB
AP-1
```

B-cell Activation, Proliferation, and Differentiation

```
CD40L
B
IL-4, IL-5, IL-6
PLA
CD40
B cell
B cell
B cell
B cell
Surface Ig
B cell
B cell
B cell
Proliferation
Differentiation and Antibody Production
```

Antibody Quantitative Response

```
Antibody MoA

IgG1
ADCC
Complement
```

Host Defense
<table>
<thead>
<tr>
<th>Antigen</th>
<th>Normal Response</th>
<th>Inappropriate Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious Pathogen</td>
<td>Host Defense</td>
<td>Recurrent/infection</td>
</tr>
<tr>
<td>Innocuous Substance</td>
<td>Allergy</td>
<td>No response</td>
</tr>
<tr>
<td>Grafted Organ</td>
<td>Rejection</td>
<td>Acceptance</td>
</tr>
<tr>
<td>Tumor</td>
<td>Tumor Immunity</td>
<td>Cancer</td>
</tr>
<tr>
<td>Normal Tissue/Organ</td>
<td>No response</td>
<td>Autoimmunity</td>
</tr>
</tbody>
</table>
Immunotherapy in Neurologic Disease
Melody Ryan, Pharm.D., MPH
University of Kentucky

Objectives

- Describe the current understanding of the pathophysiologic mechanisms of immune-mediated neurologic disease
- Evaluate the evidence and controversies for the use of immunomodulating therapy in the treatment of multiple sclerosis

Pathophysiology of MS

c. 1995
- It is an autoimmune disease
- Something bad happens to the myelin

c. 2011
- Inflammatory component
  - Responsible for relapses
- Neurodegenerative component
  - Responsible for disability

T Cells

- Adhesion molecule (α4β1-integrin) on T cells allows binding to ICAM-1 and VCAM-1 on vascular endothelial cells
- T cell transmigrates through the cells and breaches the blood-brain barrier
- T cell re-activated by an APC
- Activated T cell enters the parenchyma with help of matrix metalloproteinases 2 and 9


Th17 Cells

- IL-6, produced by activated T cells and macrophages, is important for generation of Th17 cells
- Th17 cells produce IL-6, IL-17, IL-21, IL-22, and tumor necrosis factor-α (TNF-α)

Beta Interferons

- Suppress proliferation and migration of the T cells, particularly Th17 cells
- Decreases antigen presentation by MHC class II molecules
- Decreases integrin to prevent T cell migration
- Reduces matrix metalloproteinase 9 to stabilize the blood-brain barrier
- Inhibit inflammatory cytokines increase anti-inflammatory cytokines


Beta Interferons Long-term Efficacy

- All forms effective against placebo
- 16 years worth of data with interferon β-1b
- Sustained 40% reduction in relapse rate and slower rate of disease progression in patients taking continuously compared to placebo or short-term use of interferon β-1b
- Caveat: sustained reduction in relapse rate not seen for IM interferon β-1a, but those treated earlier had better long-term outcomes


Glatiramer Acetate

- Suppress proliferation and migration of the T cells
- Induces apoptosis of T cells
- Induces a shift from Th1 to Th2 cells


Glatiramer Acetate Long-term Efficacy

- Approximately 12 years of follow-up data
- 80% reduction in relapse rate compared to baseline data
- Disability scores also improved/stayed stable in patients continuously treated compared to those withdrawn


Controversy

- Neutralizing antibodies
  - Develop in up to 44% of patients on β interferons
  - Least frequent in lowest dose and lowest frequency administered β interferons
  - If persistent, higher relapse rate
  - With time, may disappear
  - Presence correlates with reduction in MxA induction assay which also predicts relapse rates


Best Treatment Interferon vs. Interferon

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVIDENCE</td>
<td>INF-1a 44 μg SQ 3x/wk vs. INF-1a 30 μg IM 1x/wk; 24 weeks</td>
<td>Decreased relapse rate and active lesions on MRI with INF-1a 44 μg SQ 3x/wk</td>
</tr>
<tr>
<td>INCOMING</td>
<td>INF-1b 250 μg SQ QOD vs. INF-1a 30 μg IM 1x/wk; 2 years</td>
<td>Decreased relapses and active lesions on MRI with INF-1b 250 μg SQ QOD</td>
</tr>
<tr>
<td>Clanet, et al.</td>
<td>INF-1a 30 μg SQ 1x/wk vs. INF-1a 60 μg IM 1x/wk; 36 months</td>
<td>No difference between treatments in disability or rate of progression</td>
</tr>
</tbody>
</table>

Controversy

Best Treatment

Interferon vs. Glatiramer Acetate

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEYOND</td>
<td>INF β-1b 250 µg SQ QOD vs INF β-1b 500 µg SQ QOD vs. glatiramer acetate 20 mg QD; 2 years</td>
<td>No difference</td>
</tr>
<tr>
<td>REGARD</td>
<td>INF β-1a 44 µg SQ 3x/wk vs glatiramer acetate 20 mg QD; 96 weeks</td>
<td>No difference</td>
</tr>
<tr>
<td>BECOME</td>
<td>INF β-1b 250 µg SQ QOD vs glatiramer acetate 20 mg QD; 2 years; MRI study</td>
<td>No difference</td>
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Check-in Question 1

Which is the best first-line treatment for MS?
- Interferon β-1a SQ 3x/week
- Interferon β-1b SQ QOD
- Glatiramer acetate 20 mg QD
- One of these is not better than the others

Mitoxantrone

- Eliminates and deactivates monocytes and macrophages
- Inhibits T cell proliferation and migration
- Inhibits B cell activation
- Compared to placebo, decreased number of exacerbations and improved MRI parameters


Mitoxantrone - Controversy

- Cardiotoxicity
  - Dose-limiting to 140 mg/m²/lifetime
  - May not be dose-related
  - May have late-onset
  - New FDA guideline for LVEF evaluation prior to each dose

www.fda.gov

Check-in Question 2

Why is there a lifetime maximum dose for mitoxantrone?
- There is a risk of leukemia
- There is a permanent discoloration of the sclera
- There is a risk of cardiotoxicity
- There is a risk of allergic reaction

Natalizumab

- Humanized monoclonal IgG4-antibody
- Binds to α4β1-integrin so the T cell cannot bind
- Prevents the migration of the T cell into the CNS
- Reduced relapse rates by 68% (0.23/y v. 0.73/y)
- Reduced disability progression by 42% over 2 years
- Reduced new lesions on MRI by 83%

Natalizumab - Antibodies
- 9% of patients develop antibodies at some point during treatment; 6% have persistent antibodies
- 82% with persistent antibodies develop them within the first 12 weeks of therapy
- Causes decreased efficacy


Natalizumab – Progressive Multifocal Leukoencephalopathy
- Opportunistic infection caused by reactivation of the JC DNA virus
  - 50-86% of adults have antibodies to JCV
- Rapid progression and often causes death or severe disability
- Shortly after marketing, 3 cases reported and natalizumab was suspended
- Re-introduced in 2006 with a restricted distribution and extensive monitoring program


PML after Re-introduction
- Exposure of 65,000 MS patients with 28 new cases of PML
- Reporting rate = 1-2/month
- Risk is proportional to exposure duration
- Symptoms: neurobehavioral, motor, language, cognitive, or vision changes, seizures, hemiparesis, tremor


Treatment of PML
- Withdrawal of natalizumab
- Aggressive immune reconstitution
  - Plasma exchange
  - Immunoabsorption
- Immune reconstitution inflammatory syndrome
  - High-dose steroids
- Only 8 fatalities


Sphingosine 1-phosphate
- Sphingolipids are structural components of cell membranes
- Sphingomyelin is metabolized to sphingosine 1-phosphate (S1P)
- There are 5 receptors for S1P
  - S1PR1 is widespread in CNS, vascular, and immune systems
  - S1PR2 is in lymphoid tissue
  - S1PR5 is on natural killer cells and in oligodendrocytes


Sphingosine 1-phosphate
- S1P and S1PR4 controls entry and exit of naïve B and T cells into the lymphatic systems
- S1P regulates heart rate, vascular tone, and blood pressure and may have effects on pulmonary function
- S1P promotes the survival of oligodendrocytes and oligodendrocyte precursor cells (OPC) and OPC differentiation
- S1P is involved with neurite extension and retraction

Fingolimod

- S1PR modulator
  - Binds to all S1PR except S1PR2
  - Prevents the exit of naïve T cells and central memory T cells (TCM) from the lymphoid tissues
  - TCM include Th17 cells
  - Increases the number of progenitor and mature oligodendrocytes and protects them from cell death
  - Increases brain-derived neurotrophic factor


Fingolimod - Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Relapse Rate</th>
<th>Relapse-free New or Enlarged MRI Lesions (mean)</th>
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<tbody>
<tr>
<td>Fingolimod v. Placebo; 2-year study</td>
<td>1033</td>
<td>F=0.18/y</td>
<td>P=0.40/y</td>
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<tr>
<td></td>
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<td>F=74.7%</td>
<td>P=45.6%</td>
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<tr>
<td></td>
<td></td>
<td>F=2.5 P=9.8</td>
<td></td>
</tr>
<tr>
<td>Fingolimod v. Interferon β-1a IM Qweek; 1-year study</td>
<td>1153</td>
<td>F=0.16/y</td>
<td>I=0.33/y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F=82.6%</td>
<td>I=69.3%</td>
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<td>F=1.7 I=2.6</td>
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</table>


Check-in Question 3

SP is started on fingolimod. She has a CBC 1 week after beginning therapy. What do you expect the results to show?

a. Increased WBC
b. Decreased WBC
c. Increased platelets
d. Decreased platelets
e. No change

Controversy - Treatment

Escalation vs. Induction

- Escalation algorithms begin with the safest treatments and move on to more aggressive therapies only in the event of treatment failure
- Induction algorithms concentrate all therapeutic efforts on the early phases of the disease, which ultimately defines prognosis


Conclusion

- Much is now known, but much is left to learn about the role of the immune system in MS
- Several therapies are now available for treatment of MS; however, there is no consensus on the best therapy
- There is controversy regarding the place in therapy of all currently available medicines
PRO: Targeting inflammation should be a goal for the prevention and treatment of cardiovascular disease

Monday, October 17, 2011
Sheila L. Stadler, Pharm.D., BCPS
Clinical Pharmacy Specialist, Kaiser Permanente of Colorado, Aurora, Colorado; Clinical Assistant Professor, University of Colorado–Denver School of Pharmacy, Aurora, Colorado

Objectives

- Discuss the evidence for inflammatory markers and their association with various cardiovascular diseases
- Compare and contrast the evidence for treatment modalities targeting inflammation and their effect on clinical outcomes

Background

- Cardiovascular disease (CVD) is abnormal function of the heart and blood vessels
- CVD is the leading cause of death worldwide

Inflammation in Early Atherosclerosis

- Triggers of atherosclerosis can initiate expression of adhesion molecules by endothelial cells which allows attachment of leukocytes to arterial wall
- Likely culprit: vascular cell adhesion molecule-1 (VCAM-1)
- Proinflammatory cytokines provide a chemotactic stimulus to adherent leukocytes to migrate into the intima

Macrophage and Inflammation

- Monocytes transform into macrophages, express scavenger receptors, engulf lipid particles, and become foam cells
- Macrophages multiply and release proinflammatory growth factors and cytokines
T-cells and Plaque Inflammation

- Antigens presented by macrophages and dendritic cells trigger the activation of antigen-specific T cells in the artery
- Activated T cells produce Th1 cytokines (e.g., interferon-γ), which activate macrophages and vascular cells, leading to inflammation
- Regulatory T cells modulate the process by secreting antiinflammatory cytokines (interleukin-10 and transforming growth factor β)

Cytokine Cascade

- Activated immune cells in the plaque produce inflammatory cytokines (interferon-γ, interleukin-1, and tumor necrosis factor), which induce the production of interleukin-6
- Interleukin-6 stimulates the production of large amounts of acute-phase reactants, including C-reactive protein (CRP), serum amyloid A, and fibrinogen

Lipoprotein-associated phospholipase A2 (Lp-PLA₂)

- Lp-PLA₂ is an inflammatory biomarker and is directly related to propensity of plaque rupture
- Lp-PLA₂ is an enzyme that hydrolyzes oxidized phospholipids and releases lysophosphatidylcholine

Biomarkers of Inflammation proposed for diagnostic use

- VCAM-1
- IL-6
- hsCRP
- Lp-PLA₂

hsCRP for Risk Prediction

- 40-50% of those at intermediate risk according to ATP III were reclassified by the addition of hsCRP and family history to clinically relevant higher or lower risk groups

hsCRP as a Potential Therapeutic Goal

- Clinical outcomes best among statin-treated patients who not only achieved LDL-C <70 mg/dL but also achieved hsCRP <2 mg/L
- 28% lower chance of recurrent MI or vascular death


hsCRP to Target Therapy

- JUPITER trial enrolled 17,802 without CVD with LDL-C < 130 mg/dL and hsCRP ≥2 mg/L
- Randomized to rosuvastatin 20 mg or placebo
- 44% reduction in primary endpoint of all vascular events


Lp-PLA₂ as a Therapeutic Target

- Darapladib is a direct inhibitor of Lp-PLA₂
- Shown to prevent necrotic expansion of human coronary atherosclerotic plaque
- Phase III study currently recruiting: The stabilization of plaques using darapladib-thrombolysis in myocardial infarction 52 trial (SOLID-TIMI 52)

Conclusion

- There is evidence that numerous inflammatory markers are associated with CVD
- Strongest evidence lies with utilizing hsCRP for risk prediction, to identify patients who may benefit from statins, and as a potential dual goal along with LDL-C
- Lp-PLA₂ may provide information about plaque inflammation and stability and as a direct target for treatment

Rebuttal

1. Proof of concept
2. Prospective validation
3. Incremental value
4. Clinical utility
5. Clinical outcomes
6. Cost-effectiveness
Cost-Effectiveness for hsCRP

- 5 year NNT for JUPITER was 25 for primary trial end point and 32 for “hard” end point of MI, stroke, or death.
- Comparable 5 year NNT values between 86-140 have been reported as cost-effective for treatment of hypertension.

CVD continues to be the leading cause of death worldwide.

Even with treating to patients to goal for traditional risk factors, there is still residual risk.

We need to explore beyond the traditional risk factors and target inflammation for the prevention and treatment of CVD.

• Recommendations for measurement of CRP
  • Class IIa
    – In men ≥ 50 years or women ≥ 60 years with LDL-C < 130 mg/dL; not on lipid-lowering, hormone replacement, or immunosuppressant therapy; without CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or contraindications to statins, measurement of CRP can be useful in the selection of patients for statin therapy.
    – Level of Evidence: B


• Recommendations for measurement of CRP
  • Class IIb
    – In asymptomatic intermediate-risk men < 50 years of age or women < 60 years of age, measurement of CRP may be reasonable for cardiovascular risk assessment.
    – Level of Evidence: B

Targeting inflammation should **NOT** be a goal for the prevention and treatment of cardiovascular disease

Craig D. Williams, Pharm.D.
Clinical Associate Professor, Department of Pharmacy Practice
College of Pharmacy, Oregon Health & Science University, Portland, Oregon

I accept, as should we all, that inflammation plays a very important role in atherosclerosis. While hs-CRP gets most attention, the inflammatory process in atherosclerosis clearly involves multiple lines of inflammation.

But…….the question is what to do about it: “Should we target inflammation to prevent and treat CAD?” Two potential areas to target:

1. Directly target inflammation with an anti-inflammatory approach
2. Use of inflammatory biomarkers to better target anti-atherogenic therapy

“mean IMT was correlated with a higher cumulative corticosteroid intake…”

“There are conflicting data regarding the effect of biologics on atherosclerosis”

Non-steroidal, anti-inflammatory agents also clearly offer no benefit for CAD and appear to be associated with risk.

Conclusions: “Even short-term treatment with NSAIDs was associated with increased risk of death and recurrent MI……any NSAID use should be limited from a CVD safety point of view.”

And we all know the story of Vioxx and selective COX2 inhibitors….
Atherosclerosis is a lipoprotein driven process

So, the inflammation in atherosclerosis is a **RESPONSE** to the underlying disease which is subendothelial retention of lipoproteins. Treating atherosclerosis with anti-inflammatory agents is akin to treating pneumonia with prednisone.

There may even be some benefit of vascular inflammation:
- **Circulation** 2007;115:548
  - “local arterial inflammation signals the release of bone marrow-derived stem cells…that participate in the healing response of the injured blood vessel”

One area where ‘smart’ targeting of native immunity has been tried is in the elevation of HDL to retard atherosclerosis.

HDL is a particle which did not evolve as part of the traditional lipoprotein pathway but rather as part of our innate immune system (note its completely separate lifecycle from the atherogenic, apoB-containing lipoproteins)

CETP inhibition with torcetrapib in 15,067 high risk patients increased HDLc by 72% and increased total mortality by 58%

A word of caution:

- **New England Journal of Medicine** April 1st, 2004
  - “C-Reactive Protein and Other Circulating Markers of Inflammation in the Prediction of Coronary Heart Disease”
  - To minimize confounding from fluctuations in hs-CRP, this analysis performed over 12 year period on 2,459 case patients who had an MI compared to 3,696 controls who remained disease free.

2. Use of inflammatory biomarkers as prognostic factors to direct therapy

A word of caution:

- **PK Shaw, Circulation, 2000**
  - “It remains to be proven that any of the inflammatory markers provide incremental information over and above traditional risk stratification.”
The story of inflammatory cytokines in CAD is long and tortuous:

Inflammatory cytokines clearly play an important role in atherosclerosis……

May 2001

……but VCAM-1, like others has an unclear role in predicting events

Sept 2001

"no meaningful, predictive benefit of VCAM-1"

Lancet; Sept., 2001

Framingham: Many CHD Patients Have TC Below or Near Average

<table>
<thead>
<tr>
<th>TC (mg/dL)</th>
<th>Non-CHD</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>1378</td>
<td>193</td>
</tr>
<tr>
<td>200</td>
<td>219</td>
<td>244</td>
</tr>
<tr>
<td>250</td>
<td>41</td>
<td>51</td>
</tr>
</tbody>
</table>

To determine if biomarker add utility to clinical risk prediction: Ten commonly cited biomarkers (including hs-CRP, fibrinogen and PAI-1) were applied to the Framingham database

Conclusion: No added predictive benefit

NEJM; Dec 2006

Conclusion:
1. So while hs-CRP, VCAM-1, IL-6, IL-8, WBC and other inflammatory markers have been found to be associated with atherosclerosis, their role in practice as targets of drug therapy or predictors of events in individual patients is suspect at best
2. Atherosclerosis induces an inflammatory response but the disease process is accumulation of lipoproteins in the arterial wall and the appropriate treatment strategy is lowering of those atherogenic lipoprotein (e.g. LDL) particles (just like the treatment for pneumonia is antibiotics, not prednisone)

Rebuttal

Curricular Track I—The Role of the Immune System in Disease Pathophysiology: Implications for Pharmacotherapy

Absolute Risk Reduction (ARR) from 0.85 to 0.40 gives an annual NNT of 250.

I have no complaint with the "cost-effectiveness of generic statins in a "JUPITER-like" population but traditional risk factors are as prognostic as an hs-CRP and how much more generic statin could you use at your institution for the cost of an hs-CRP test?
What really predicts CVD? CRP (Cash in Ridker’s Pocket) or Framingham risk?

Ridker, NEJM 2002;347:1557

Donald Lloyd-Jones; NLA meeting, 2007

Rebuttal Conclusion:

Our job as clinicians is to understand and treat the causes of disease. For atherosclerosis, that includes lipid lowering, BP control, smoking cessation, antiplatelet therapy and glycemic control where appropriate.

Anti-inflammatory agents have no proven role in treating or preventing CAD and anti-inflammatory biomarkers have not been proven to add prognostic value to traditional risk scoring tools.