Vasculitis

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CME Disclosure Statements
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Unlabeled use of commercial products
To date, there is only one therapeutic agent that is
FDA approved for the treatment of any form of vasculitis

All other references to use of a commercial product discussed
in this presentation constitute an unlabeled use of the product

Speaker relationship to products discussed in this presentation
Genentech
Bristol-Myers Squibb provide study drug for clinical trials
on which the speaker is an investigator
Biologic Therapies in Vasculitis - 2013

For certain forms of vasculitis, biologic agents have become a valuable treatment option

Interest in biologics in vasculitis remains high in whether they may:
- Interrupt pathophysiologic mechanisms involved in disease
- Reduce disease relapses
- Decrease glucocorticoid requirements
- Provide a therapeutic alternative to current approaches

Publications using biologics in vasculitis continue to increase
But … most of these consist of case reports and case series

Before using a biologic agent in clinical practice we must broadly examine the benefits, risks, and goals

Issues to Weigh When Considering Use of a Biologic Agent in a Patient with Vasculitis

- The effectiveness of current standard therapy
- What is the goal for using a biologic agent in a specific patient
- Strength of the safety and efficacy data in that setting

- Randomized trial
- Prospective open-label study
- Retrospective report

Today’s discussion will examine the data in:

Giant cell arteritis
Granulomatosis with Polyangiitis (Wegener’s)
Giant Cell Arteritis

1950
Prednisone + Aspirin
Improves symptoms
Reduces risk of blindness

2013
Prednisone + Aspirin
Relapse 75-90%
Toxicity 35-86%

Current Treatment
Potential Disease Mechanisms in GCA

Evidence of GCA as an antigen driven disease

- Macrophages
- Dendritic cells
- T lymphocytes

• Brack et al. Mol Med 1997;3:530
• Weyand, Goronzy. NEJM 2003;349:160

Evidence of tissue production of pro-inflammatory cytokines (TNFα, IL-6, IL-1β) in temporal arteries

• Weyand et al. A&R 1997; 40:19
• Hernández-Rodríguez et al. Rheum 2004; 43:294

Infliximab in Giant Cell Arteritis


Enrolled 44 patients with newly diagnosed GCA

- Primary Endpoint: proportion of relapse-free subjects through week 22
- Safety Endpoint: incidence of adverse events
**Infliximab in Giant Cell Arteritis**


**Efficacy:**
Proportion of Relapse-Free Subjects through Week 22
No difference in cumulative prednisone dose

**Safety:**
Infection:
- 71% infliximab
- 56% placebo

Strengths and Limitations:
- Size of study and dose of infliximab could have missed modest effects of infliximab
- Risk would not be justified to achieve only a small benefit of infliximab

*Infliximab does not provide benefit in the treatment of GCA*

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**Infliximab in Polymyalgia Rheumatica (PMR)**


**Methods:**
- 51 patients with newly diagnosed PMR
- All received prednisone 15mg/d tapered to 0 mg/day over 16 weeks
- Randomized 1:1: infliximab 3mg/kg at weeks 0, 2, 6, and 22 vs placebo

**Results:**
No difference in placebo and infliximab:
- Relapse/recurrence at 52 weeks
- Relapse/recurrence at 22 weeks
- Proportion off steroids at week 22
- Total number relapse/recurrence
- Duration of prednisone
- Dose of prednisone
- Adverse events – 8 in each group

*Infliximab does not provide benefit in the treatment of PMR*
IL-6 in GCA

IL-6 has been of longstanding interest in GCA

Utility as a acute phase reactant – variable

- Roche et al. A&R 1993;36:1286
- García-Martínez et al. AC&R 2010;62:835

Expression and production in GCA tissue

- Hernández-Rodríguez et al. Rheum 2004;43:294

Could this provide a novel means for treatment of GCA?

Tocilizumab in GCA

Experience with tocilizumab is currently based solely on case reports

<table>
<thead>
<tr>
<th>Study</th>
<th>GCA</th>
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<tbody>
<tr>
<td>Nishimoto et al. 2008</td>
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<td>Beyer et al. 2011</td>
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<td>Sciascia et al. 2011</td>
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<td>Salvarani et al. 2012</td>
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<td>Besada et al. 2012</td>
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<td>Unizony et al. 2012 *</td>
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<td>Lurati et al. 2012</td>
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<td>Işık et al. 2012</td>
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<td>Bravo Mancheño et al. 2012</td>
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<tr>
<td>Xenitidis et al. 2013 *</td>
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<td>Total</td>
<td>23</td>
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- Overall a beneficial response has been observed
- What does reduction of acute phase reactants mean with this agent?
- 2 reports (*) have found ongoing vascular inflammation despite treatment

Efficacy of anti-IL-6 in GCA is currently unknown
A randomized trial is being planned in GCA (www.clinicaltrials.gov)
Abatacept in GCA

T cell activation has been felt to play an important role in GCA.

Concurrent Studies of Abatacept in GCA and TAK (AGATA)
- Multicenter, randomized withdrawal design trial – conducted by VCRC
- www.clinicaltrials.gov
- Trial is ongoing and open for enrollment

There is no current clinical role for abatacept in GCA

Granulomatosis with Polyangiitis (Wegener’s) - GPA
(Formerly Wegener’s Granulomatosis)

- Granulomatous inflammation
- Vasculitis
- Glomerulonephritis
GPA (Wegener’s) – Treatment 2001 - 2011

**Remission**

**Induction (3-6 months)**
- Severe Disease: Cyclophosphamide + GC
- Non-severe Disease: Methotrexate + GC

**Maintenance (at least 2 years)**
- Methotrexate
- Azathioprine
- (Mycophenolate mofetil)

**Severe Disease**
- Remission
- Prolonged survival
- Remission > 85%

**Non-severe Disease**
- Relapse 50-70%
- Toxicity

**GPA (Wegener’s)**
- Granulomatous Inflammation
Use of Etanercept in GPA (Wegener’s)

**Wegener’s Granulomatosis Etanercept Trial (WGET), NEJM 2005; 352:19**

- **Standard Therapy**
  - Prednisone with taper
- **Randomization**
  - Etanercept
  - Placebo

0 3 6 // Close of trial

Objectives:
- Induction
- Maintenance

**Results:**
- Etanercept: 69.7%
- Placebo: 75.3%
- P=0.39

- 180 patients
- Objective: determine the efficacy of etanercept to sustain remission
- Sustained remission > 6 months
  - Etanercept 69.7%
  - Placebo 75.3%

Does not support the use of etanercept in the treatment of GPA
Current evidence does not support the use of any anti-TNF agent in GPA.


32 pts with ANCA-associated vasculitis (GPA=19, MPA=13)
16 pts Rx with infliximab+daily CYC+prednisone
16 pts with refractory disease infliximab added to current treatment

- 88% achieved remission
- 18% relapsed
- 6% mortality (pulmonary hemorrhage, pneumonia)
- 21% serious infections

Similar to Crohn’s - could other anti-TNF agents be effective in GPA?

GPA (Wegener’s)
Potential Pathogenic Mechanisms

Could inference with this pathway through the B cell provide a means for therapeutic intervention?

ANCA target antigens:
Proteinase 3 (PR3)
Myeloperoxidase (MPO)

ANCA-induced Neutrophil mediated vascular injury
Cyclophosphamide vs Rituximab for Remission Induction (RAVE)

Stone et al. NEJM 2010; 363:221

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<thead>
<tr>
<th>OR (Blinded)</th>
<th>Azathioprine</th>
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<tr>
<td>Rituximab (375mg/M2/week x 4 weeks)</td>
<td>Prednisone</td>
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Primary Endpoint = in remission and off prednisone at 6 months

197 ANCA (+) GPA or MPA
Meeting primary endpoint
All patients: RTX 64%, CYC 53% (p<0.001)
Relapsing patients: RTX 67%, CYC 42%

Rate of adverse events: RTX = CYC
Severe relapse: RTX 6%, CYC 10%
Mortality rate: 2% (1 RTX, 2 CYC)

For remission induction, rituximab is as effective as cyclophosphamide
This was the basis for FDA approval of RTX for GPA/MPA in April 2011

CYC vs Rituximab for Remission Induction (RITUXVAS)

Jones et al. NEJM 2010; 363:211

<table>
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<tr>
<th>CYC</th>
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<td>IV CYC</td>
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VERSUS

<table>
<thead>
<tr>
<th>RTX</th>
<th>RANDOMIZED 3:1 RTX:CYC-AZA (Non-Blinded)</th>
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<td>IV CYC x 2</td>
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Primary Endpoint = sustained remission (BVAS=0 for 6 months)

44 ANCA (+) GPA or MPA, new dx
Hypothesis: RTX better than CYC
Primary endpoint: RTX 76%, CYC 82%

Rate of adverse events: RTX = CYC
Mortality rate: 18% (6 RTX, 2 CYC)
- Median age 68, 20% dialysis
- GFR: RTX 20, CYC 12 ml/min

Rituximab was effective but was not superior to cyclophosphamide
Rituximab (RTX) in GPA (Wegener’s)

Remission induction

**Question**
Rituximab is as effective as cyclophosphamide for remission induction of severe disease – does that mean it should be used to induce remission in everyone?

**No** – there is not strong data for use in all populations

**Remission induction**
- Relapsing severe disease
- Newly diagnosed severe disease
- Non-severe relapse, occurring on methotrexate
- Non-severe relapse, never received methotrexate
- Newly diagnosed non-severe disease
- Fulminant disease (creatinine > 4.0, mechanical ventilation)

**Strength of evidence for use**
- Strong
- Weak

Relapses do occur after rituximab so determining a plan for remission maintenance needs to be considered in each patient

**Options**
- Conventional maintenance agent (MTX, AZA, MMF)
- Scheduled repeat rituximab infusions (how often? how much?)
- Close clinical observation and retreat with rituximab for relapse

**What has been learned from the published literature?**
Rituximab (RTX) in GPA (Wegener’s)

Cartin-Ceba et al. A&R 2012; 64:3770
• Single center observational study of those who received ≥ 2 RTX courses
• 53 patients, 233 courses of RTX
• retreatment - for relapse (85 courses) or B cell repletion (148 courses)
• median number of RTX courses 4 (2-12 courses)
• all but 9 courses were 375 mg/m²/week x 4 weeks
• no evidence of resistance over time to RTX
• toxicity: 2 Deaths - 1 Pneumocystis, 1 AML, late onset neutropenia
• decline in IG noted but not tied to infection occurrence

Strengths and Limitations:
– retrospective
– only those with relapsing disease not controlled with standard therapy
– experience with multiple infusions

Rituximab (RTX) in GPA (Wegener’s)

Smith et al. A&R 2012; 64:3760
• Retrospective study in 73 patients comparing two periods in time:
  – (A) 2002-2006 RTX 375mg/m²/wk x 4 wks followed until relapse
  – (B) 2006-onwards RTX 375mg/m²/wk x 4 wks then 1g q6 mos x 2 yrs

• Outcome Group A
  – 85% relapsed
  – in remission: 60% at 12 months, 20% - 24 months, 10% - 48 months
  – 33% who relapsed were still B cell depleted

• Outcome Group B
  – 12% relapsed within the 24 months while on scheduled RTX
  – 21% relapsed after RTX stopped at 24 months
  – trend towards lower IG levels

Strengths and Limitations:
– retrospective study over 2 different time periods
– incomplete follow-up
– concomitant therapies
– insights of experience with scheduled infusions
**Rituximab (RTX) in GPA (Wegener's)**

**Remission maintenance after rituximab induction**

There are still many areas of uncertainty

- Is scheduled rituximab better than a conventional maintenance agent?
- If the decision is made to use scheduled rituximab:
  - How often should infusions be given?
  - What dose should be given?
  - Are there markers than can guide when to retreat?
  - When can scheduled rituximab be lengthened out or stopped?

Current clinical decisions are individualized based on:

- Past treatment history
- Toxicity to treatment
- Relapse history
- Damage from past disease (need to avoid relapse)

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**GPA (Wegener's) – Treatment Options In 2013**

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<th>Maintenance (at least 2 years)</th>
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Factors to take in consideration in determining treatment:

- Level of disease severity
- Initial disease or relapse
- Medication contraindications
- Past treatment history
Biologic agents have been beneficial in certain vasculitides
Use in clinical practice must be weighed based on data and goals
The investigation of biologic therapies in vasculitis is essential