ANTI-TNFs: When to use?
Who gets it?
Special Populations

Psoriatic Arthritis (ACR Guidelines: first line agents)
Cardiovascular Disease
Complications: HS, Crohn's, UC, PG
Subpopulations: Elderly, Hepatitis C, HIV +, Pregnancy/Lactation

FDA Approved Biologics
Etanercept 2004
Infliximab 2006
Adalimumab 2008
Golimumab 2009
Certolizumab 2013
Ustekinumab 2013
Secukinumab 2015
Ixekizumab 2017
Brodalumab 2017
Tildrakizumab 2018
Risankizumab 2019

Psoriasis

HOW DO I CHOOSE?
Etanercept 2003
Infliximab 2004
Adalimumab 2005
Golimumab 2009
Certolizumab 2013
Ustekinumab 2013
Secukinumab 2015
Ixekizumab 2017
Brodalumab 2017
Tildrakizumab 2018
Risankizumab 2019

Disclosures
A管理制度: Investigator; Sponsor; Bureau; Investigator; Grants
Columbia: Investigator; Sponsor; Bureau; Investigator; Grants
Sponsor: Investigator; Bureau; Investigator
Novartis: Investigator; Sponsor; Bureau; Investigator
Janssen Biotech: Investigator; Sponsor; Bureau; Investigator
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Ortho Dermatologic: Investigator; Sponsor; Bureau; Investigator
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6/23/19
How do I decide to start a patient on a systemic therapy?

- BSA?
- Quality of life issues?
- Previous therapy?
- Response to previous therapy?
- Did patient fail to respond to topicals or not a candidate?
- Long term safety & efficacy data
- Special Considerations

SAFETY AND EFFICACY OF ANTI-TNFs

Prior anti-TNFs do not affect responses
Standard for comparators to other agents
Safe & FDA approved for young patients
Often preferred therapy to start
Often covered by Medicare/Advantage plans

Long term safety & efficacy
May be cardioprotective
Improves insulin resistance
Reduces inflammatory biomarkers

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OBJECTIVE:
- To examine the safety and efficacy of anti-tumor necrosis factor (TNF) agents (etanercept, infliximab and adalimumab) in HIV-positive patients with rheumatic diseases refractory to standard therapy.

METHODS:
- CD4 count of ≥200 mm3 and an HIV viral load of <60 000 copies/mm3 and no active concurrent infections.
- Changes in CD4 counts, HIV viral loads, or other adverse effects while on anti-TNF agents and clinical response were monitored for 28.1 (SD 20.9) months (range 2.5-55).

RESULTS:
- Eight HIV-positive patients were treated with anti-TNF blockers. No significant clinical adverse effect was attributed to this treatment in any patient.
- CD4 counts and HIV viral load levels remained stable in all patients.
- Three patients on etanercept therapy and two patients on infliximab had sustained clinical improvement in their rheumatic diseases.

Use of anti-tumor necrosis factor therapy in HIV-positive individuals with rheumatic diseases.

- 27 patients mostly with rheumatic disorders were treated with TNF inhibitors.
- Authors propose that TNF-alpha inhibitors can be used in patients treated with ART and stable CD4 count.
- Physicians should work closely with infectious disease specialists for monthly monitoring of CD4 T-cell counts and viral load.
- If CD4 counts decrease, ART adjustment should be considered and antiretroviral treatment changed accordingly.
- Patients should be screened for latent tuberculosis. If indicated, they should be given standard prophylaxis before initiation of therapy.
- There is no clear relationship between CD4 count and infectious complications; therefore no strict cutoff should be recommended.
TNF-α inhibitors in psoriatic arthritis and concomitant hepatitis C virus infection.

INTRODUCTION: TNF-α inhibitors in psoriatic arthritis and concomitant hepatitis C virus infection.

METHODS: Double-blind, randomized, placebo controlled trial. Fifty patients with chronic HCV were randomly assigned to receive interferon alfa-2b and ribavirin with either etanercept or placebo for 24 weeks. The main outcome measure was the absence of HCV RNA at 24 weeks, the on treatment response at the end of the etanercept randomization period.

RESULTS: At 24 weeks, HCV RNA was absent in 63% (12/19) etanercept patients compared to 32% (8/25) placebo patients (P=0.04). In addition, patients receiving etanercept had lower frequency of most adverse events categories compared to placebo.

CONCLUSIONS: Etanercept given for 24 weeks as adjuvant therapy to interferon and ribavirin significantly improved virologic response at the end of the etanercept randomization period among patients with HCV, and was associated with decreased incidence of most adverse effects associated with interferon and ribavirin.

Hepatitis C

INTRODUCTION: Review literature on efficacy and safety of anti-TNF-α agents in PsA and concomitant HCV infection.

EXPERIMENTAL DESIGN: To find all cases of PsA and concomitant HCV infection treated with TNF-α inhibitors.

RESULTS: 38 cases of patients with PsA and concomitant HCV infection in therapy with anti-TNF-α agents.

CONCLUSIONS: Data suggest that therapy with the anti-TNF-α agents, mainly etanercept and adalimumab, at least with short-term use, would appear efficacious and reasonably safe in the management of PsA patients with concomitant HCV infection.


REFERENCES:

Long term safety & efficacy data

Adalimumab

more than 15 years

diverse range of indications,

dynamic data highlighting the safety and efficacy of adalimumab in head to head trials.

FDA approved: Ps; PsA; RA; AS

Crohn’s Disease, IBD

Phase 3 studies

Adalimumab from 18 clinical trials in adult patients with moderate-to-severe plaque psoriasis


No new safety signals

More than 20 years of experience

Long term safety good

Slight increase in infections

No signal for increase in Ca

Pediatric Crohn’s

Medicare coverage

Infliximab

No new safety signals

More than 20 years of experience

Long term safety good

Slight increase in infections

No signal for increase in Ca

Multiple indications

Pediatric PsA

Medicare coverage

Faster response

Pediatric Crohn’s

Journal of Drugs in Dermatology 2014. 13 (12):1441

PASI RESPONDER RATES BY VISIT THROUGH WEEK 48

Pregnancy*

Studies show that exposure to biologics during the first trimester: no increased risk of congenital defects compared with the general population. **

No teratogenicity

No increased risks of infections in newborns

Certolizumab does not cross placenta barrier

Available data are mostly from gastroenterology and rheumatology (de Lima et al., 2015; Foger & Villiger, 2016).

Kurizky et al., 2015; Marchioni & Lichtenstein, 2013; Mervic, 2014).

** And T, Thomsen SF. Dermatol Ther. 2017

ELISA ANALYSIS OF ANTI-TNF LEVELS FROM MATERNAL BLOOD, UMBILICAL CORD BLOOD, AND INFANTS ON DAY OF BIRTH FROM MOTHERS RECEIVING TREATMENT FOR INFLAMMATORY BOWEL DISEASE

Study 1 (Mahadevan, et al.): An Assessment of 3 Anti-TNFs, Demonstrating Low Placental Transfer of Certolizumab

Study 2 (CRIB): Certolizumab Demonstrated Negligible to Low Placental Transfer

Study 3 (CRADLE): Minimal Transfer of Certolizumab Into Breast Milk

Pharmacokinetic studies assessing placental transfer

STUDY 1
- McLeod: Assessed the placental transfer of multiple anti-TNFs

STUDY 2
- CRIB: Measured the level of placental transfer of Certolizumab from mothers to infants

STUDY 3
- CRADLE: Determined the concentrations of Certolizumab in mature breast milk throughout the dosing interval and calculated the average daily infant dose of maternal Certolizumab

Pharmacokinetic studies assessing breast milk transfer

These pharmacokinetic studies are designed to assess transfer of drug from mother to infant in breast milk. No conclusions regarding safety and efficacy can be made

Study 2 (CRIB): Certolizumab Demonstrated Negligible to Low Placental Transfer of Certolizumab

- Plasma Certolizumab concentrations in mothers and infants (N=15 mother-infant pairs)

- Certolizumab concentration (µg/mL)

- Delivery (±24 hours)

- Week 4 (±7 days; two samples not collected)

- Week 8 (±7 days)

- Mothers

- Infants

- LLOQ=0.032 µg/mL

- Certolizumab concentrations were not measurable in 13 of 15 infants at birth

- At Weeks 4 and 8, there were no measurable Certolizumab concentrations in any infant

Study 3 (CRADLE): Minimal Transfer of Certolizumab Into Breast Milk

- Breast Milk Certolizumab Concentration (n=17)

- Maternal Certolizumab Concentration: 15.7 µg/mL

- Max = 0.076 µg/mL

- Certified by IACUC (Institutional Animal Care and Use Committee)
**Pregnancy Outcomes in Anti-TNFs**

13 studies: (RA, IBD)

- Anti-TNF users had non-significant trend towards reduced rate of live birth
- Increased risk of preterm birth, spontaneous abortion and low birth weight
- Risk of anomalies was not elevated
- No increased pregnancy related complications

**Long term safety & efficacy data**

**Certolizumab**

- More than 20 years experience
- Durable response
- Multiple indications
- No new safety signals
- Similar efficacy in Prior biologic exposure
- Long term safety & efficacy data
- Certolizumab
- 'For Her'

**HOW DO I CHOOSE?**

**First Choice**

- Any anti-TNF
  - Adalimumab; infliximab; certolizumab
  - Adalimumab; infliximab

**Insurance call**

- Etanercept; adalimumab; infliximab
- Certolizumab
- Infliximab