Conventional and biologic therapy in spondyloarthritiscan stop both inflammation and new bone formation?

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Dear Donkey

Please go slowly and we are friends. Please not let me falling down because I am already at the age of osteoporosis.
Spondylopathy

Pre-axial SpA

Ankylosing Spondylitis

Juvenile SpA

Arthritis associated with Crohn's disease / UC

Undifferentiated SpA

Reactive arthritis Reiter syndrome

Psoriatic Arthritis

Sacroiliitis

Uveitis
The concept of Spondyloarthritis

Spondylarthropathies (SpA)

**Sub-group**

- Ankylosing spondylitis
- Psoriatic arthritis
- Reactive arthritis
- IBD related arthritis
- Undifferentiated SpA

**Clinical presentation**

- Axial involvement
- Peripheral articular involvement
- Enthesopathy
- Extra-articular features
Ankylosing & Psoriatic spondylitis

- Acute inflammation
- Chronic inflammation
- Bone destruction
- Bone formation
- Syndesmophyte
- Ankylosis
General Features of SpA

- Inflammatory back pain
- Peripheral arthritis, usually asymmetric
- Enthesitis
- Dactylitis
  - Less common than enthesitis
  - More common in PsA
- Uveitis
  - Usually acute, anterior, unilateral, and recurrent
DIP Disease

Enthesitis

Dactylitis

Mutilans
Psoriasis vulgaris (plaque type)
Prevalence of IBP... in back pain

IBP = Inflammatory back pain
MBP = Mechanical back pain

85%
15%

# Prevalence of IBP in spondyloarthritis

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>Prevalence of axial involvement</th>
<th>Ref. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory bowel disease</td>
<td>5 to 12%</td>
<td>1</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>20 to 40%</td>
<td>1, 3</td>
</tr>
<tr>
<td></td>
<td>up to 78%</td>
<td>3, 4</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>100% (?)</td>
<td>5</td>
</tr>
<tr>
<td>Spondyloarthritis (ESSG study)</td>
<td>75%</td>
<td>6</td>
</tr>
</tbody>
</table>

4. Richtlin CT. Rheumatology 4th, ed. 2008;1183-8
5. Reveille J. Rheumatology, 4th ed. 2008:1109-18
Inflammatory back pain (IBP)

- **Traditional definition**
  At least four of the following
  - Morning stiffness
  - Improvement with exercise
  - Insidious onset
  - Persistence for $\geq 3$ months
  - Younger than 40 years at onset
  Calin A. JAMA 1977;237:2613

- **New proposal**
  At least two of the following
  - Morning stiffness lasting longer than 30 minutes
  - Improvement with exercise but not by rest
  - Awakening with pain in the 2nd half of the night
  - Alternating buttock pain
Final set of classification criteria for axial SpA selected by the ASAS

ASAS classification criteria for axial SpA
(in patients with back pain ≥ 3 months and age at onset < 45 years)

**Sacroiliitis on imaging***

- plus
- ≥ 1 SpA feature**

or

**HLA-B27**

- plus
- ≥ 2 other SpA features**

**SpA features:**
  - Inflammatory back pain
  - Arthritis
  - Enthesitis (heel)
  - Uveitis
  - Dactylitis
  - Psoriasis
  - Crohn's disease/ulcerative colitis
  - Good response to NSAIDs
  - Family history for SpA
  - HLA-B27
  - Elevated CRP

* Sacroiliitis on imaging:
  - Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
  - Or
  - Definite radiographic sacroiliitis according to mod. New York criteria

Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic back pain and age at onset < 45 years.

Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%.

** Note: Elevated CRP is considered a SpA feature in the context of chronic back pain
Concept of pre-radiographic axial SpA

Sieper et al

Pre-radiological stage
(axial undiff. SpA)

Back pain

ATLAS

Radiological stage

Mod. New York Criteria 1984

Back pain

Radiological Sacroiliitis

Back pain

Syndesmophytes

Time (years)
Paramount importance of synovial tissue
Macrophage

Proinflammatory cytokines
Degradation of cartilage and bone

bone erosion
higher expression of MMP-3 in AS than OA in the synovial LL, and more prominent CD68+ cells observed in AS than OA in the synovial SL. These results suggest that MMP-3 and CD68 cells may play an important role in the pathogenesis of synovial inflammation in AS.
Axial SPA = \( \mathbb{1} + \mathbb{2} \)

1. Non-radiologic SPA + Low back pain with normal sacroiliac joint

2. Radiologic SPA (AS) AS with hip arthritis and total hip replacement
Clinical relevant biomarkers in AS

Brunn J. Nat Rev Rheumatol 2012:8:8-10

(1) Inflammation
   CRP, IL6, VEGF

(2) Bone & cartilage destruction
   MMP3, Cathepsin K,

(3) New bone formation
   Scleostin, DKK1, bone alkaline phosphate
Primary goal in management of AS

- Inflammation
- Structure change
- Mobility
- Function
Axial spondyloarthritis including AS

(Inflammatory) back pain

Stage 1  Stage 2  Stage 3

Sacrollitis (MRI)  Radiographic changes due to sacrollitis (NY criteria)  Radiographic changes due to spondylitis (syndesmophytes)

Spondylitis (MRI)

uSpA
Axial uSpA
Pre-radiographic AS
Non-radiographic AS

Ankylosing spondylitis
## Goals of Treatment in AS

<table>
<thead>
<tr>
<th>Symptomatic control</th>
<th>Disease control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce pain &amp; stiffness</td>
<td>rapid and sustained control of inflammation</td>
</tr>
<tr>
<td></td>
<td>Improvement of spinal mobility and function</td>
</tr>
<tr>
<td></td>
<td>Prevention of structural damage</td>
</tr>
<tr>
<td></td>
<td>Prevention of disability</td>
</tr>
<tr>
<td></td>
<td>Remission</td>
</tr>
<tr>
<td></td>
<td>healing</td>
</tr>
</tbody>
</table>
## Conventional vs Biologics

<table>
<thead>
<tr>
<th>Conventional</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>DMARDs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>Immunosuppressives</td>
<td>Golimumab</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
</tr>
</tbody>
</table>
ASAS/EULAR recommendations for the management of AS

Education, exercise, physical therapy, rehabilitation, patient associations, self help groups

NSAIDs

Axial disease

Peripheral disease

Sulfasalazine

Local corticosteroids

TNF blockers

Analgesics

Surgery

## NSAID

<table>
<thead>
<tr>
<th>COX1/COX1</th>
<th>COX1/COX2</th>
<th>COX2/COX2</th>
</tr>
</thead>
<tbody>
<tr>
<td>✢ Volteran</td>
<td>✢ Mobic</td>
<td>✢ Celebrex</td>
</tr>
<tr>
<td>✢ Naproxan</td>
<td>✢ Nimed</td>
<td>✢ Arcroxia</td>
</tr>
<tr>
<td>✢ Sulindac</td>
<td>✢ Lonin</td>
<td></td>
</tr>
<tr>
<td>✢ Indomethacin (Acemet)</td>
<td>✢ Relifex</td>
<td></td>
</tr>
<tr>
<td>✢ Surgem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✢ Ketoprofen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Dosage of NSAIDs Used to Treat Ankylosing Spondylitis

<table>
<thead>
<tr>
<th>drug</th>
<th>half-life (hours)</th>
<th>approved maximal daily dosage (mg)</th>
<th>normally for arthritis-</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceclofenac*</td>
<td>about 4</td>
<td></td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>8-12</td>
<td></td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>Diclofenac*</td>
<td>about 2</td>
<td></td>
<td>125-150</td>
<td></td>
</tr>
<tr>
<td>Etoricoxib#</td>
<td>about 22</td>
<td></td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.8-3.5</td>
<td></td>
<td>2400-3200</td>
<td></td>
</tr>
<tr>
<td>Indomethacin*</td>
<td>about 2</td>
<td></td>
<td>150-200</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>1.5-2.5</td>
<td></td>
<td>200-300</td>
<td></td>
</tr>
<tr>
<td>Meloxicam</td>
<td>about 20</td>
<td></td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>10-18</td>
<td></td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Phenylbutazone#</td>
<td>50-100</td>
<td></td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>Piroxicam</td>
<td>30-60</td>
<td></td>
<td>20</td>
<td></td>
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</tbody>
</table>

*retard formula available  
# not approved in the US

Adapted from Song IH et al. Arthritis Rheum 2008;58:929-38
NSAIDs are rather efficacious in AS

<table>
<thead>
<tr>
<th>COX2</th>
<th>Trial</th>
<th>Duration</th>
<th>No. of patients</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celebrex</td>
<td>Naposin</td>
<td>12 week</td>
<td>611</td>
<td>BASDAI, pain decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400mg=naposin</td>
</tr>
<tr>
<td>Celebrex</td>
<td>Volteran</td>
<td>12 week</td>
<td>458</td>
<td>pain decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200=400=volteran</td>
</tr>
<tr>
<td>Acroxia</td>
<td>Naposin</td>
<td>52 week</td>
<td>387</td>
<td>spinal pain decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90=120=naposin</td>
</tr>
</tbody>
</table>
NSAID reduce radiographic progression in patient with AS
Conventional DMARDs Are Largely Not Effective for the Treatment of Patients with AS

**Sulfasalazine**  
2 g/day

**Leflunomide**  
20 mg/day

**Methotrexate**  
20 mg/week sc

ASAS-Recommendations for the Treatment of AS Patients with TNFα-Blockers

Correct Diagnosis of AS (‘usually’ mod. New York Criteria)

- at least 2 NSAIDs over 3 months
- 2-3 g sulfasalazine over 4 months
- local steroid injections if indicated

High disease activity: BASDAI ≥ 4

Predominant peripheral manifestations

Predominant axial manifestations

plus

Positive expert opinion based on parameters such as:

- Positive CRP/ESR
- Positive MRI
- Radiological Progression
- Clinical examination

Changes of Synovial histopathology after anti-TNFα therapy in SPA

Infliximab (5mg/kg) 0, 2, 6 weeks
8pts, 3AS, 1USPA, 4PSA

Results: at week 12
↓ SLL hyperplasia
↓ CD 53+ Synoviocytes
↓ Vascularity
↓ VACM-1
↓ PMN, CD68 + M
↓ CD4 T cells

Baeten D, Arthritis Res 2001;44:186
Results

1. Abundant synovial expression of RANKL & OPG in SPA
2. Decreased RANKL expression in patients with good response to TNF α blockade
**Responder biomarkers after infliximab for AS**

Romen-Sanchez C et al, Clin Rheumatol 2008:27:1429

1. 2 weeks after infliximab, the combination of ESR, CRP and platelet count distinguish responders from non-responder (81.3% sensitivity vs 72.7% specificity)

2. Serum IL1α

R vs NonR at week 6 (sensitivity 84.9%, Specificity 53.8%)
Monoclonal Antibodies

Soluble TNF receptors

Normal interaction

Neutralization of cytokines

Inflammatior cytokine

Cytokine receptor

Inflammatory signal

Monoclonal antibody

Soluble receptor

No signal
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Certolizumab</th>
<th>Golimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name</td>
<td>Remicade</td>
<td>Humira</td>
<td>Enbrel</td>
<td>Cimzia</td>
<td>Simponi</td>
</tr>
<tr>
<td>Dosing</td>
<td>Q6W-8W</td>
<td>Q2W</td>
<td>BIW</td>
<td>Q4W</td>
<td>Q4W</td>
</tr>
<tr>
<td>Dose</td>
<td>3-5 mg/kg</td>
<td>40mg</td>
<td>25mg</td>
<td>400mg</td>
<td>50mg</td>
</tr>
<tr>
<td>Routes</td>
<td>I.V</td>
<td>S.C</td>
<td>S.C</td>
<td>S.C</td>
<td>S.C</td>
</tr>
<tr>
<td>Company</td>
<td>Centocor</td>
<td>Abbott</td>
<td>Wyeth</td>
<td>UCB (Euro)</td>
<td>Centocor</td>
</tr>
<tr>
<td>Mab</td>
<td>Chimera</td>
<td>Human</td>
<td></td>
<td>Humanized, Fab, Peg.</td>
<td>Human</td>
</tr>
<tr>
<td>FDA</td>
<td>Approved 1998</td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
</tr>
</tbody>
</table>
四種生物製劑

- Etanercept (Enbrel 恩博）
  作用快、皮下注射 2次/星期

- Adalimumab (Humira 復邁）
  皮下注射 1 次/ 2星期

- Infliximab (Remicade)
  血管注射 1次/ 1-2個月

- Golimumab
  皮下注射 1 次/ 1個月
生物製劑優於傳統免疫調節劑

1) 作用快(2星期-1個月)
2) 作用強
3) 可有效抑制骨關節磨損破壞及關節變形
4) 可減少關節破壞所需要之外科手術(包括人工關節)
Indication of biological agents in spondyloarthropathy

Uncontrolled
- AS axial & peripheral arthritis
- Psoriasis
- PSA axial & peripheral arthritis
- Uveitis
- Enthesopathy, dactylitis
- Crohn’s disease
- Reactive arthritis
- USPA
Long-term (2 Years) Efficacy of TNFα-Antagonists in Patients with Ankylosing Spondylitis*

*Different studies, no head to head comparison

**Infliximab (ASSERT)**

- Weeks: 0, 24, 48, 72, 96
- N = 201, 199, 166

**Etanercept**

- Weeks: 0, 12, 24, 36, 48, 60, 72, 96
- N = 138, 128, 95

**Adalimumab (ATLAS)**

- Weeks: 0, 26, 52, 78, 104
- N = 311, 296, 261

N = number of patients on therapy

Antibodies to infliximab and adalimumab are related to reduced clinical response in AS

**Infliximab:**
Percentage of patients fulfilling ASAS-20 response criteria at week 54

**Adalimumab:**
Percentage of patients fulfilling ASAS-20 response criteria at week 24

ASAS: ankylosing spondylitis assessment scale

Clinical and Imaging Efficacy of Infliximab in HLA–B27–Positive Patients With Magnetic Resonance Imaging–Determined Early Sacroiliitis

Nick Barkham, Helen I. Keen, Laura C. Coates, Philip O'Connor, Elizabeth Hensor, Alexander D. Fraser, Lorna S. Cawkwell, Alexander Bennett, Dennis McGonagle, and Paul Emery

Figure 1. Magnetic resonance images of the sacroiliac joints of a patient before (A) and after (B) receiving infliximab therapy. The extensive bone marrow edema that was observed in both sacroiliac joints before treatment was resolved in the posttreatment scan.
Anti- TNFα therapy in AS

- PAIN (V)
- FUNCTION (V)
- SPINAL MOBILITY (V)
- Quality of life (V)
- ↓ ESR, ↓ CRP (V)
- Persistence (V)
- MRI (V)
- Syndesmophyte (?)
Clinical remission and response by duration of adalimumab exposure

Ns for ASAS 5/6 = 309, 297, 281, 260, and 232, respectively
Observed data
van der Heijde, et al. SAT0273
Anti-TNF-α therapy in enthesitis

- Short-term of randomized trail (12, 24 weeks) showed significant improvement of AS with enthesitis
- Open-label Rhapsody trial showed 122 of 173 AS had resolution of plantar fasciitis after adalimumab
Anti-TNF-a therapy in uveitis

- All 3 TNF-a inhibitors reduced the frequency of uveitis flares
- Adalimumab=Infliximab> etanercept
Clinical efficacy of etanercept

Multicentre, open-labeled study of Etanercept in the treatment of patients with ankylosing spondylitis in Taiwanese

2006-2007

16 centers, 23 sites, 46 AS patients

Etanercept 25mg Biw x 3 months

Efficacy: primary endpoint – ASAS 20

secondary endpoint – ASAS 50, ASAS 70, BASFI, BASDAI, global assessment
### Table Summary of ASAS response over time

<table>
<thead>
<tr>
<th>(Response)</th>
<th>Week2</th>
<th>Week4</th>
<th>Week8</th>
<th>Week12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAS 20</td>
<td>71.7%</td>
<td>87.0%</td>
<td>87.0%</td>
<td>91.3%</td>
</tr>
<tr>
<td>ASAS 50</td>
<td>34.8%</td>
<td>58.7%</td>
<td>63.0%</td>
<td>71.7%</td>
</tr>
<tr>
<td>ASAS 70</td>
<td>13.0%</td>
<td>28.3%</td>
<td>37.0%</td>
<td>45.7%</td>
</tr>
<tr>
<td>Partial Remission</td>
<td>13.0%</td>
<td>30.4%</td>
<td>41.7%</td>
<td>49.3%</td>
</tr>
</tbody>
</table>

Mod Rheumatol 2010 (accepted)
Table Summary of the changes on major outcome measure

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Outcome measures</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASAS component</strong></td>
<td>Patient global assessment</td>
<td>73.72±16.50</td>
<td>24.17±23.72</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>72.65±16.88</td>
<td>21.50±23.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>BASFI</td>
<td>57.80±24.87</td>
<td>20.45±21.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
<td>67.34±22.53</td>
<td>22.07±21.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Acute-phase reactant</strong></td>
<td>CRP level (mg/dl)</td>
<td>2.82±3.21</td>
<td>0.51±2.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>ESR (mm/hour)</td>
<td>35.73±23.13</td>
<td>7.76±7.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Spinal mobility measure</strong></td>
<td>Modified Schober test (cm)</td>
<td>2.11±2.76</td>
<td>2.58±3.42</td>
<td>0.0079</td>
</tr>
<tr>
<td></td>
<td>Chest expansion (cm)</td>
<td>2.77±1.69</td>
<td>3.56±1.82</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>Occiput-to wall (cm)</td>
<td>6.59±7.14</td>
<td>5.32±6.65</td>
<td>0.0006</td>
</tr>
<tr>
<td><strong>BASDAI</strong></td>
<td></td>
<td>68.18±16.54</td>
<td>21.60±20.44</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table: The comparison of the efficacy within 3 months treatment of different anti-TNF therapies between Caucasian and Chinese.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Caucasian</th>
<th>Chinese (China)</th>
<th>Chinese (Taiwan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>59% (28%-P)-ASAS20</td>
<td>84%-ASAS20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% (9%-P)-BASDAI</td>
<td>70%-BASDAI</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>60% (23%-P)-ASAS20</td>
<td>73.3%-ASAS20</td>
<td>90%-ASAS20</td>
</tr>
<tr>
<td></td>
<td>57% (6%-P)-BASDAI</td>
<td></td>
<td>49%-PR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>79.8%-ASAS20(Korea)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>58.2% (20.6%-P)-ASAS20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Van der Heijde: A&R 2006:54;2130
Conclusion

• Better clinical response of anti-TNFα therapy was observed in Chinese than in Caucasian with AS

• The long-term efficacy in Chinese is unknown

• Optimal dosage and relapse rate after stop of anti-TNFα agent in Chinese needs to be identified
僵直性脊椎炎病患使用Humira之人數及時間

<table>
<thead>
<tr>
<th>使用Humira時間</th>
<th>人數</th>
</tr>
</thead>
<tbody>
<tr>
<td>使用Humira&lt;1年</td>
<td>19</td>
</tr>
<tr>
<td>使用Humira 1~2年</td>
<td>33</td>
</tr>
<tr>
<td>使用Humira 2~3年</td>
<td>4</td>
</tr>
<tr>
<td>使用Humira &gt;3年</td>
<td>2</td>
</tr>
<tr>
<td>總人數</td>
<td>58</td>
</tr>
</tbody>
</table>
Results  Comparison of clinical and laboratory data in AS patients before and after 12 weeks of adalimumab treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>First M</th>
<th>2nd M</th>
<th>3rd M</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASDAI</td>
<td>8.08 ±0.92</td>
<td>4.61±0.75</td>
<td>3.85±0.60</td>
<td>3.10±0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BASFI</td>
<td>3.35±2.13</td>
<td></td>
<td>2.05±1.47</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VAS</td>
<td>7.85±1.20</td>
<td></td>
<td></td>
<td>3.555±1.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESR</td>
<td>45.78±21.90</td>
<td>12.33±15.08</td>
<td>9.74±11.70</td>
<td>8.14±10.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP</td>
<td>3.232±2.19</td>
<td>0.58±0.65</td>
<td>0.47±0.49</td>
<td>0.46±0.40</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Do we need to treat ankylosing spondylitis patients with “total spinal ankylosis” with TNF $\alpha$ blockers
Effect of TNF blockers on new bone formation -- AS

• Although TNF blockade also strongly suppresses signs and symptoms in SpA, clinical trials have thus far **failed to** show any inhibitory effects on new bone formation and ankylosis.

---

**Etanercept**


**Infliximab**


**Adalimumab**

Inefficacy, anti-infliximab antibody in SPA

1. After infliximab
   29% detect antibody after one year injection- low responder

2. After adalimumab
   For AS, 31% had antibody after 6 M injection- low responder
   For RA, 13% had antibody (related with MTX concomitantly use)

3. After etanercept
   No antibody detectable

By Irene van der Horst, Netherlands, 2011, IGAS meeting
LORHEN: Drug survival in RA is better with etanercept

The risk of TB is higher for patients receiving infliximab or adalimumab than those receiving etanercept.

如何選擇不同之生物製劑

• (1) 藥物之副作用
• (2) 藥物使用之方便性
• (3) 藥物維持之穩定性
• (4) 病患之前是否有感染病 (如 結核等)
Approach to the AS patients who fails a TNFα antagonist

(1) Back pain due to degenerative or mechanical factors
   -- Spinal compression fractures
   -- Spondylolisthesis, disc herniation
   -- Spinal stenosis, myelopathy

(2) Back pain due to infection

(3) Back pain due to malignancy

(4) Back pain due to psychiatry or fibromyalgia
TNF Failure in AS

Consider NSAIDs, intra-articular injections, physiotherapy, analgesics, gabapentin, anti-depressants, DMARDs for peripheral arthritis

TNFα not contraindicated

Switch TNFα or increase dose

Thalidomide or iv pamidronate

TNFα contraindicated

Thalidomide or iv pamidronate
Anti-TNF $\alpha$ for syndesmophyte
New therapy in AS

• Anti IL17
• Anti IL6R
• Usterkinumab
• Abatacept
• Rituximab
• Anti-BMP
• Anakinra
Possible biologics in PsA

- Anti-IL15
  - *Curr Opin Pharmacol.* 2004
- Rituximab
- Apremilast (oral phosphodiesterase-4 inhibitor)
- Tocilizumab
- Janus kinase (JAK inhibitor)
- Denosumab (RANK ligand inhibitor)
抗腫瘤壞死因子 風險管理

1) 感染 (結核或潛在結核)
結核菌皮下試驗 (PPD) >5 or >10mm
γ干擾素 (Quantiferon)
Positive intermediate
Negative

2) B型肝炎
B肝帶原，且HBV DNA 高 需治療
抗B肝核心體抗體 (Anti-HBC) 陽性
生物製劑何時退場

1) 進場容易，退場難
2) 目前無一定之規範
3) 逐漸減藥或注射時間拉長
4) 個人經驗
5) 國外之經驗，停藥後復發率仍高
高價之生物製劑：
台灣未來是否有低價之生物製劑市場？

1) 大陸
國外進口，恩利(台灣恩博)$375/一次注射
國內生產，益塞普$64.5/一次

2) 台灣
國外，恩博$150/一次注射
國內，仍未上市(效果及安全性未知)

3) 韓國
三星
結論

生物製劑治療之原則與優點

➢ The early, the better 早鳥有蟲吃
➢ One stone, 3 birds 一石三鳥(作用快，作用強，作用久)
Captain Chou Was almost “dead” in the Dead Sea