

Updating the therapeutic strategy in Rheumatoid Arthritis: what is effective, what is changing in daily practice regarding the use of DMARDs and biological agents.

The Romanian experience

C. Codreanu, Assoc Prof MD PhD  
Center of Rheumatic Diseases  
Bucharest, Romania

# RA Prevalence in Romania

- No local data available
- The estimated prevalence of RA is 0.5 –1%  
( around 150,000 patients)
- In 2008, 20,000 patients were hospitalized for RA in Romania

# RA: Advances in treatment

- Major advances in the treatment of RA have been seen during the last decade:
  - Joint damage occurs early
  - Early use of DMARDs prevents accumulation of damage
  - Better treatment strategies are able to improve outcomes
- Goals of RA treatment are remission or low disease activity and prevention of structural damage
- Introduction of biologic agents ( TNF blockers)

# EULAR Recommendations for the Management of RA With Synthetic and Biological DMARDs

- **No 1:** Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made
- **No 3:** MTX should be part of the first treatment strategy in patients with active RA
- **No 8:** In patients responding insufficiently to MTX ... biological DMARDs should be started; current practice would be to start a TNF inhibitor

# Do TNF Antagonists Meet Today's Requirements for Effective RA Therapy?

## **Highly Effective in DMARD-Resistant RA:**

- Signs and symptoms
- Radiographic progression
- Disability & health related QoL

# Romanian guidelines for biological agents

- Based on EULAR endorsed guidelines, adapted to national conditions, mandatory for all Romanian rheumatologists
- provide a management plan, giving clear inclusion/exclusion and response criteria
- Recommendations applicable for the prescription of biological agents in RA, PsA, AS

# Treatment in RA

## First line therapy

Methotrexate  
7,5-20mg/wk

Leflunomide  
20mg/day

Sulfasalazine  
2-3g/day

HCQ  
400mg/day

Gold Salts, Ciclosporine 3-5mg/kg/day  
Azathioprine 100mg/day

## Second line therapy

- Active RA (DAS28>5,1), ESR>28mm/h, CRP>20mg/l, morning stiffness >1h, despite
  - previous treatment with minimum 2 DMARDs, for at least 12 wks each

### TNF blockers:

Infliximab, Etanercept, Adalimumab

**Non-responders switch to one or more TNF alfa blockers  
or to Rituximab**

Certolizumab , Golimumab Tocilizumab, Abatacept  
Are available but not reimbursed

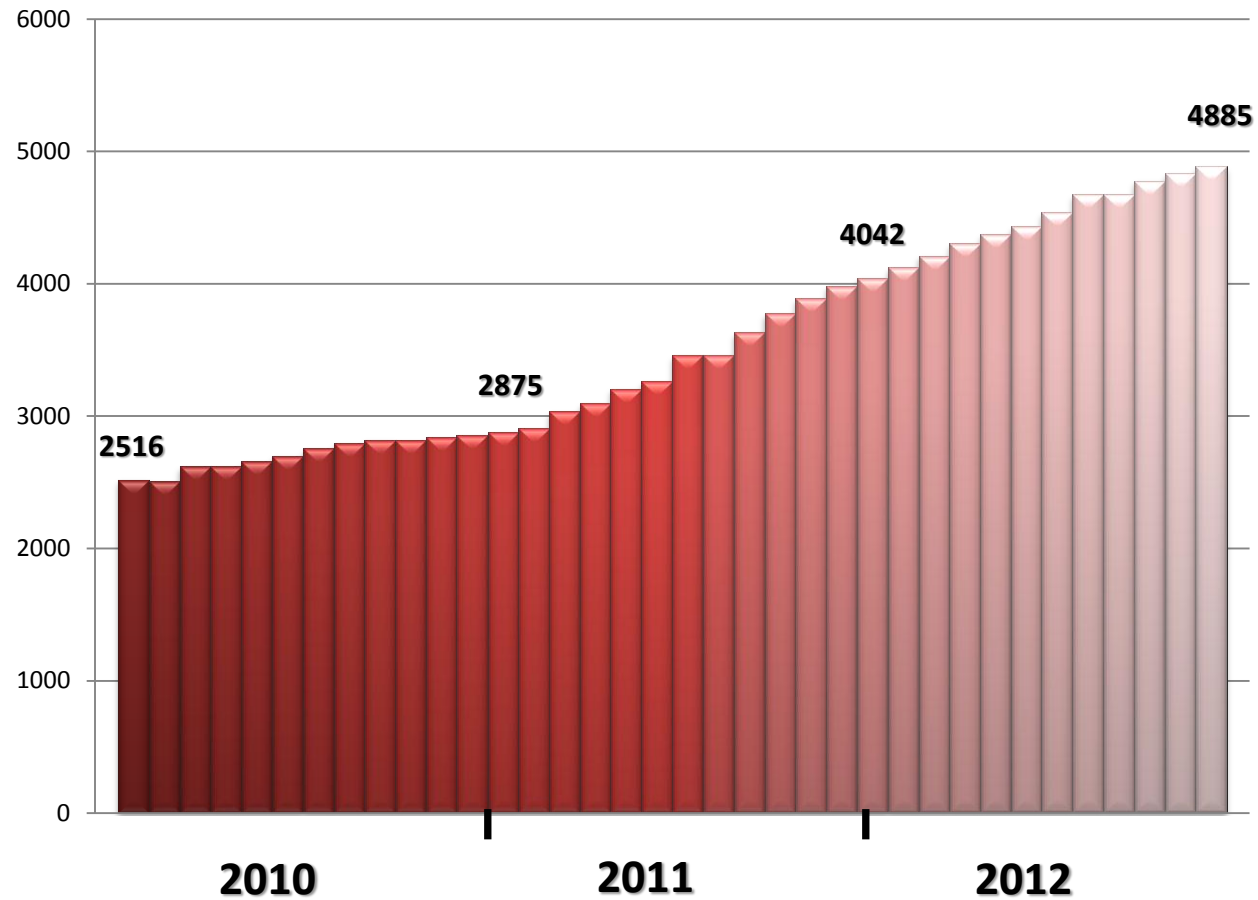
# Total Number of Patients treated with Biologics in Romania (2012) \*

<b>RA</b>	<b>4885</b>
<b>AS</b>	<b>1859</b>
<b>PsA</b>	<b>913</b>
<b>JIA</b>	<b>127</b>
<b>TOTAL</b>	<b>7108</b>

\* Data from National Health Insurance House



# Total number of RA patients treated with Biologics in Romania



\* Data from National Health Insurance House

# Romanian guidelines

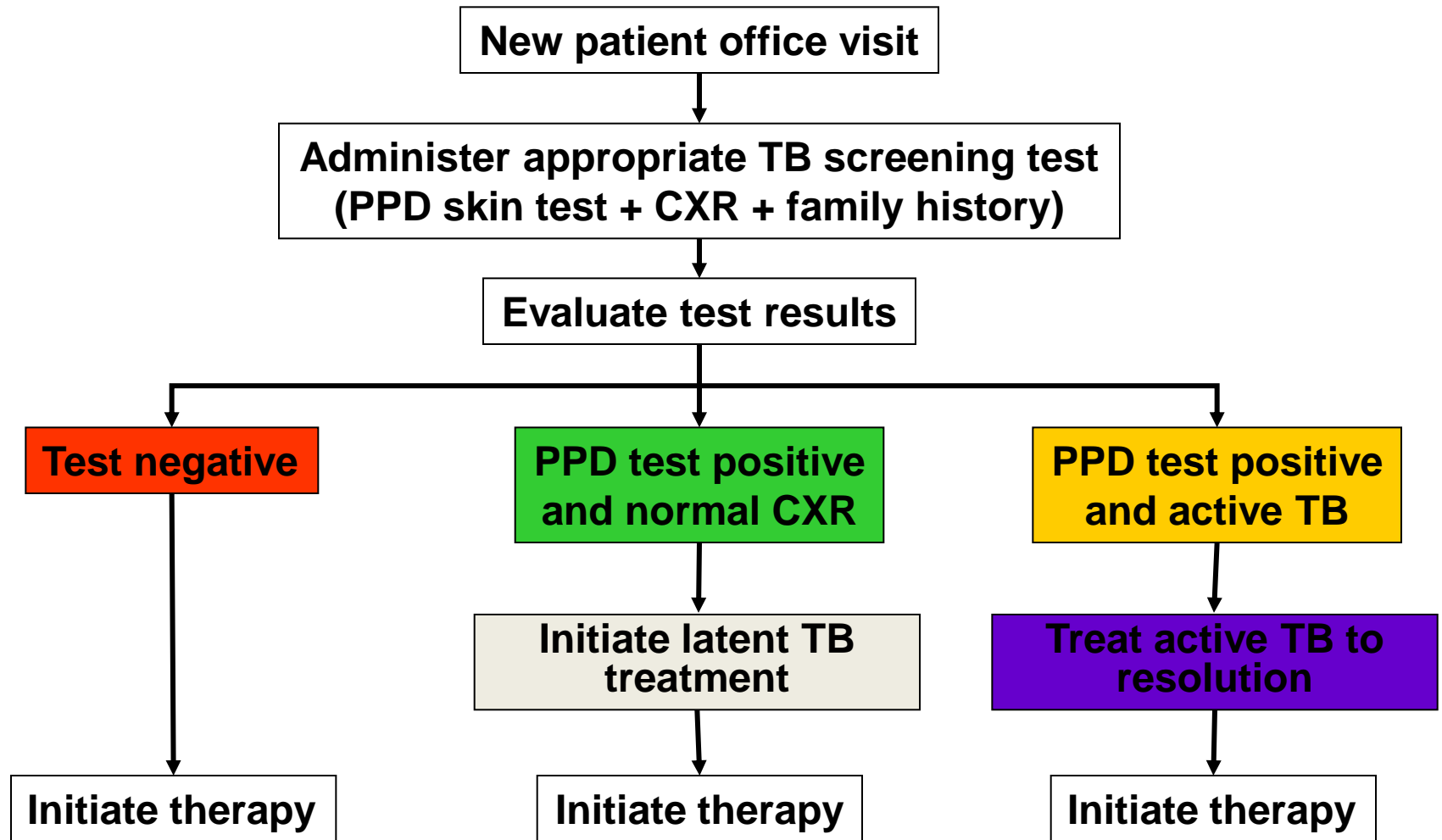
## Inclusion criteria for anti TNF therapy in RA

- **Active and severe RA defined as :**
  - DAS28 >5.1, including >5 swollen and tender joints plus 2 of the 3 criteria:
    - Morning stiffness >60 minutes
    - ESR >28mm/h
    - CRP>20mg/l
- **Treatment with 2 classical DMARDs for at least 12 weeks each, in maximum tolerated dosages is required prior to recommending a TNF blocker;**  
*(MTX is the first DMARD option, except proven contraindications!)*
- **Positive expert opinion for the initiation of anti TNF therapy**

# Exclusion criteria for anti TNF therapy in RA

- Severe infections:  
sepsis, active TB, opportunistic infections  
before treatment -TB screening is mandatory !!
- Heart failure (NYHA III/IV)
- History of hypersensitivity to infliximab, etanercept, adalimumab
- Gravidity
- Children between 0-17 years of age (infliximab)
- Lupus or lupus-like syndrome
- Any contraindications known for the TNF  $\alpha$  blockers
- Hepatitis B virus infections

# Algorithm for TB screening: European-Based Recommendations



# Anti TNF therapy and tuberculosis in Romania

2000 – 2004 (screening TB wasn't mandatory in Romania)

- 345 patients treated with Infliximab
- 22 cases of TB

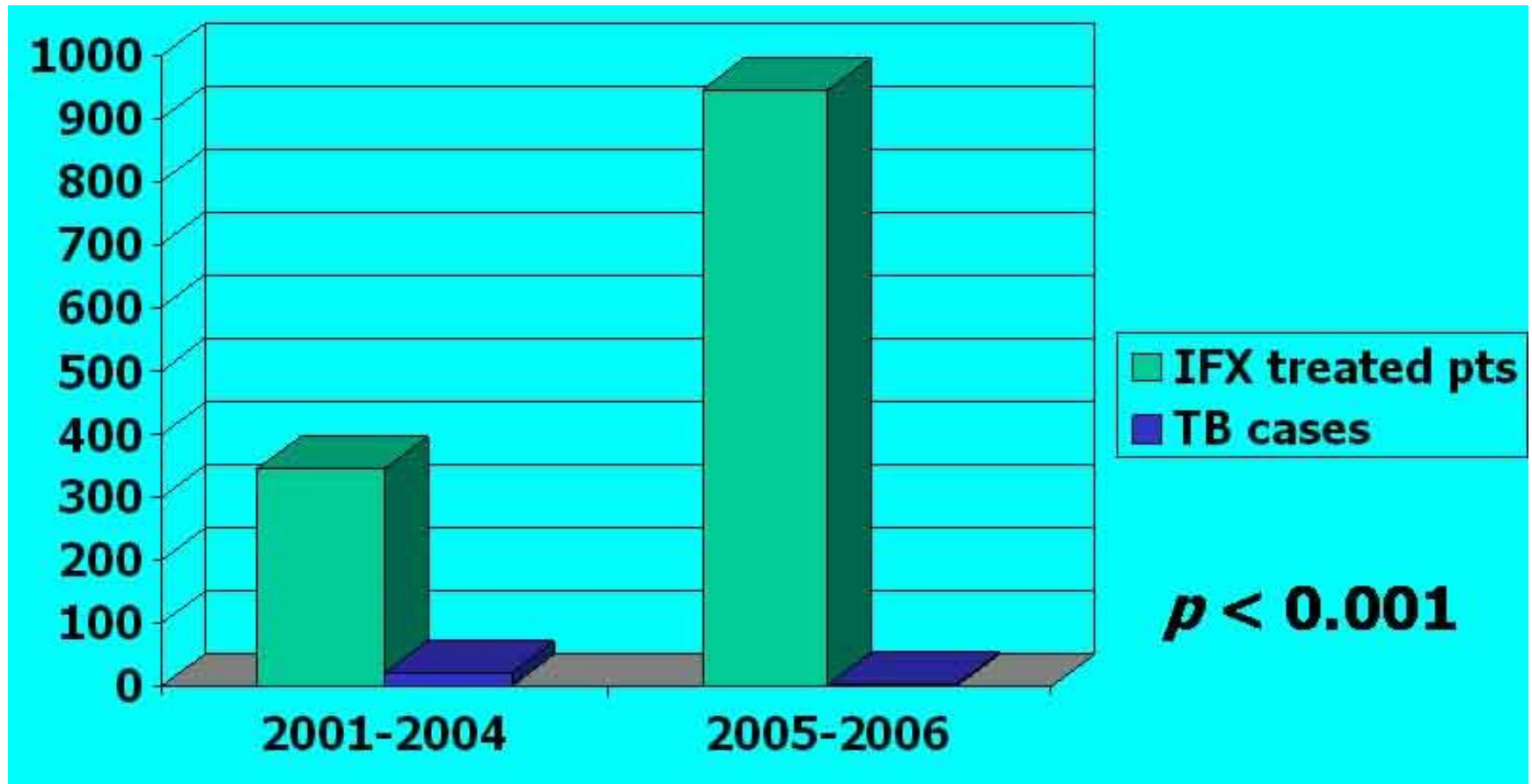
In 2005 screening for TB became mandatory!

***TB screening and exclusion of patients with latent TB generated a ten times reduction of TB cases!***

# TUBERCULOSIS IN RA PATIENTS TREATED WITH INFLIXIMAB – THE ROMANIAN EXPERIENCE

A. Balanescu, M. Bojinca, D. Bumbacea, Bojinca, D. Opris, F. Berghea, D Predeteanu, R. Ionescu

Arthritis Rheum, 2006, 54 (9S),S405



**Fig. 12 Rates of TB cases in IFX treated RA pts. pre- and post-screening. A significant reduction has been obtained (6.36% vs. 0.52%,  $p < 0.001$ )**

# TB screening started in Sept 2009

Preferred strategy by pneumologist:

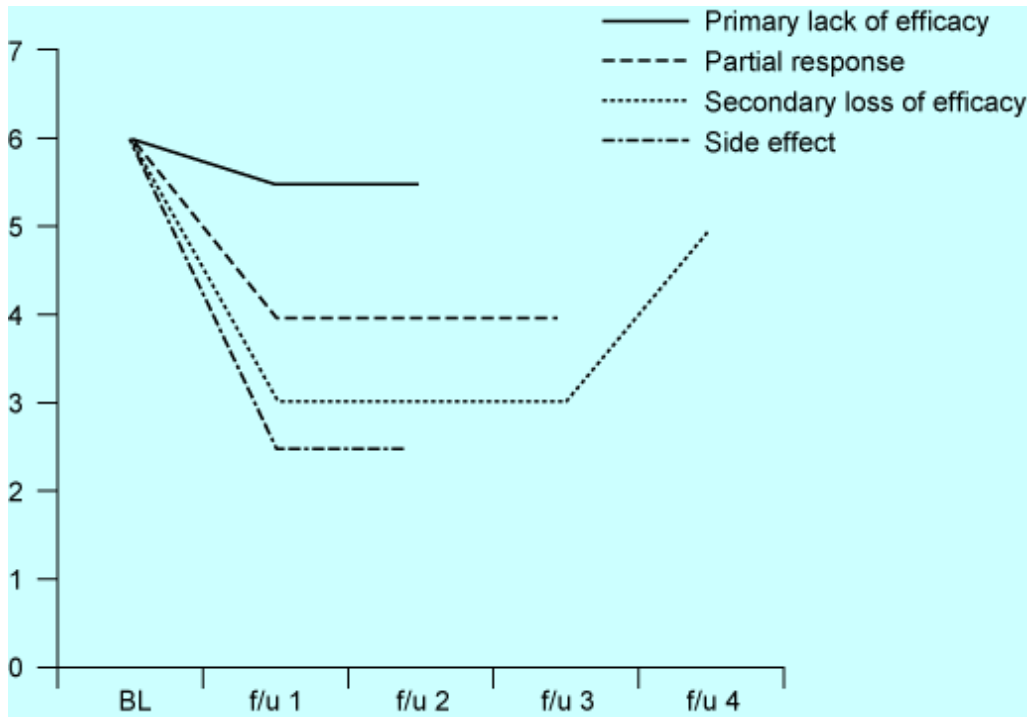
- QuantiFERON-TB Gold In Tube instead of PPD skin test
  - more sensitive than PPD skin test in detecting LTBI
  - are not influenced by BCG vaccination

# Outcome assessment for continuing anti TNF therapy

- ❑ Is done after 6 month of treatment
- ❑ Takes into consideration: DAS28, ESR, CRP  
***Responder is defined a patient with a DAS 28 improvement  $> 1,2$  or  $DAS28 < 3,2$  and 50% decrease of ESR or CRP***



# Various types of TNF failure



<b>Primary lack of efficacy</b>	<b>Patients with no clinically relevant benefit</b>
<b>Partial response</b>	<b>Patients with partial ( incomplete ) benefit</b>
<b>Secondary loss of efficacy</b>	<b>Patients with clinically relevant benefit, but lost in time</b>
<b>Side effect</b>	<b>Patients with clinically relevant benefit, but stopped therapy due to side effect</b>

# Switch Between Biologics

In patients with a suboptimal response to the initial anti-TNF treatment a switch to another biologic agent (another TNF-  $\alpha$  inhibitor or a drug with an alternative mode of action) is required and can lead to an improved response



# Inadequate response to anti-TNF therapy: what are the options?

Switch to another anti-TNF agent?

- Etanercept
- Infliximab
- Adalimumab
- Golimumab
- Certolizumab

Initiate treatment with a biological agent with a different mechanism of action?

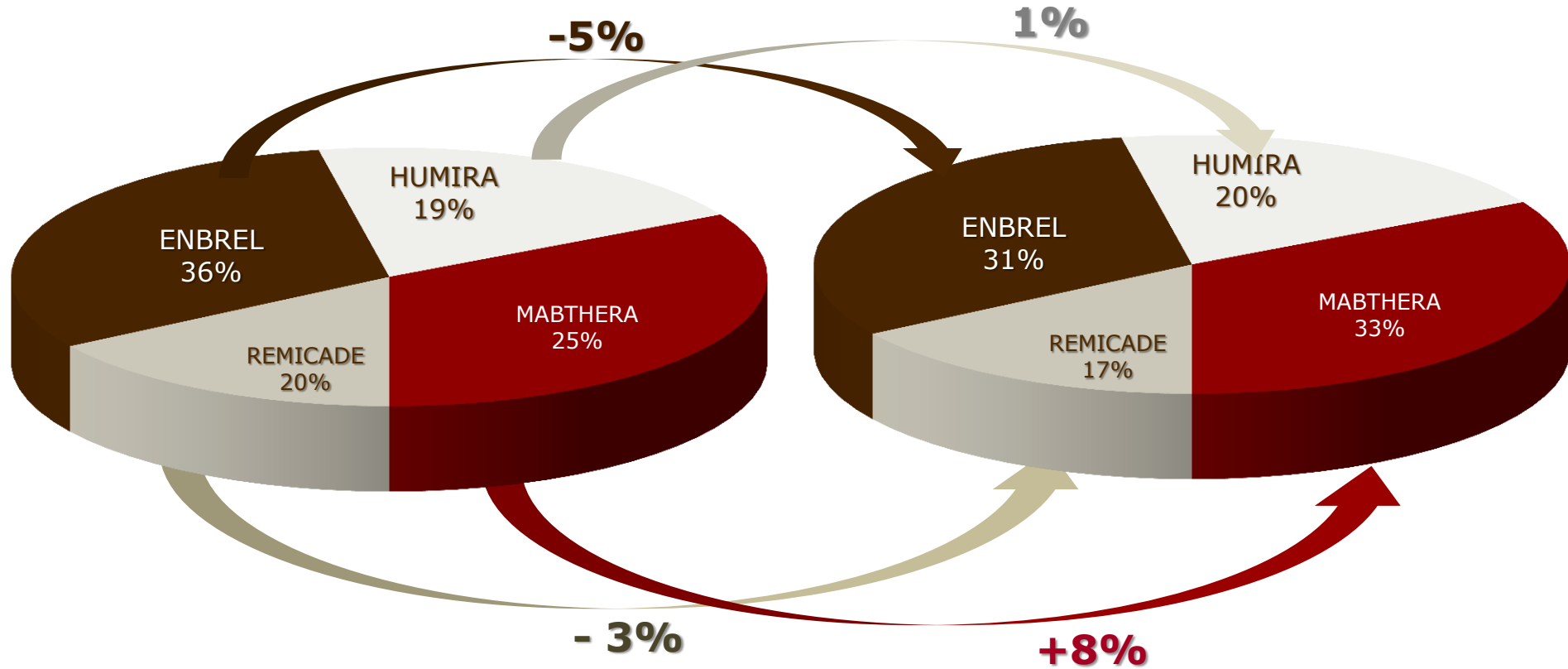
- Rituximab
- Tocilizumab
- Abatacept
- Anakinra

# RA Biologic Market by Brands Market Share Pts - NIH Shared Data

Dec 2010

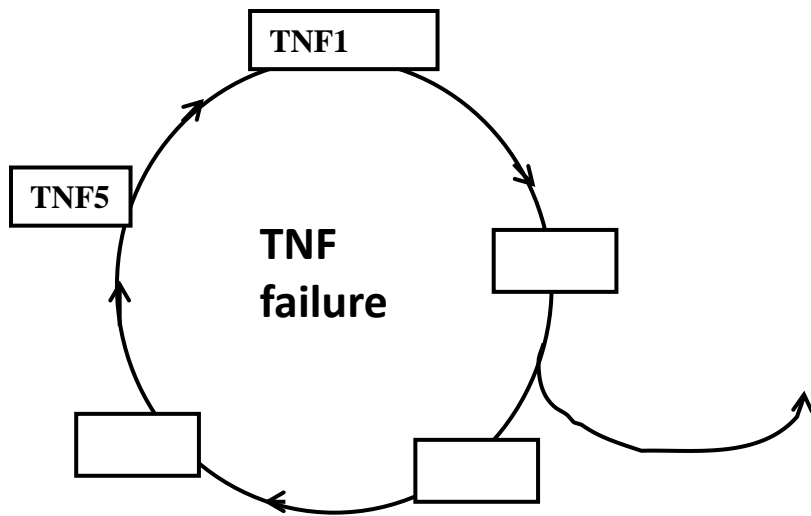
VS

Dec 2012

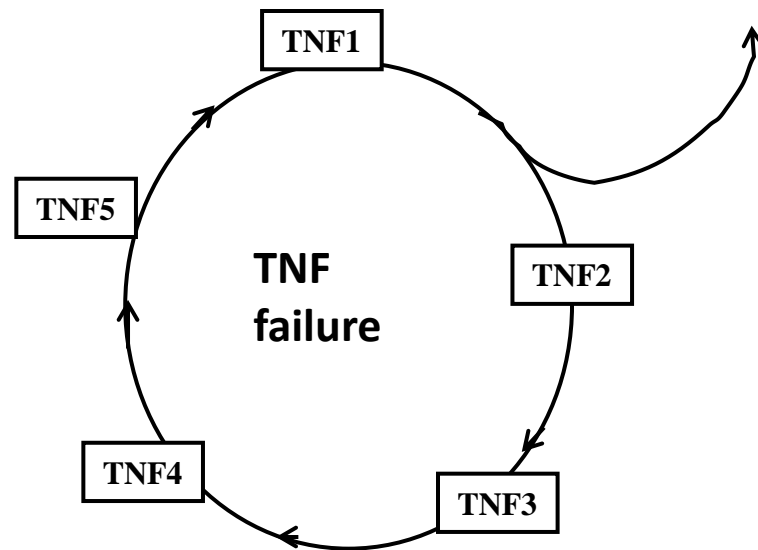


# To “wheel” or NOT to “wheel”?

## Cycling



## No cycling



# Management of RA

The ultimate goal of RA treatment:  
**'Remission'**

- Remission
  - Clinical
  - Radiographic/US/MRI
- Low disease activity

**New Strategies**

**Better Tools**

- Early treatment
- Intensive approach for monitoring & therapy will give better results
- We need to set targets and adapt/change therapy to achieve goals

**Early & aggressive use of combined treatments with biologics could modify the natural history of RA**

