THE CLINICAL IMPACT OF DRUG IMMUNOGENICITY

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IMMUNE-MEDIATED CHRONIC INFLAMMATORY DISEASES

- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Psoriasis and Psoriatic Arthritis
- Inflammatory Bowel Diseases
- Multiple Sclerosis

Prevalent Diseases

Chronic (no cure)

Highly disabling

Affecting young people (in productive age)

HIGH SOCIAL AND ECONOMIC IMPACT

PARADIGM SHIFT IN TREATMENT

FROM SMALL MOLECULES TO LARGE PROTEINS

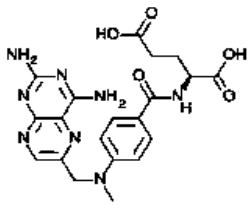
Synthetic DMARs

Therapeutic Targets

TNF CD20 B7.1/2 IL-6

1992

Metothrexate
Hidroxicloroquina
Salazopirina
Corticosteroids



BIOLOGIC DMARDS

- ✓ Better control of inflammation
- ✓ Improvement in patient's quality of life
- ✓ Improvement in patient's functionality

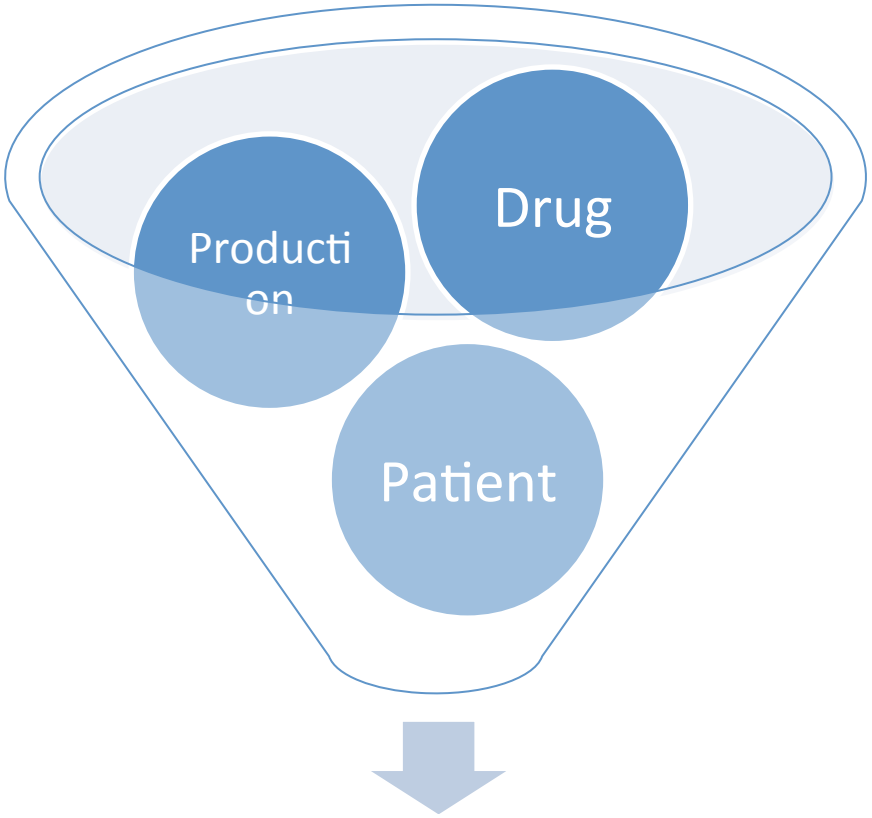
BIOLOGICALS MIGHT INTERFERE WITH HOMEOSTASIS

Replicates of natural compounds synthesized by the organism, but administered at doses far above physiological concentrations of their natural equivalents

Variations from steady state (homeostatic conditions) may alert the immune system

Adaptive Immune Responses

Drug Immunogenicity: the ability that virtually all therapeutic proteins have to elicit an immune response against themselves



Unwanted Immunogenicity

PROBLEM: HIGH HETEROGENEITY IN CLINICAL RESPONSES

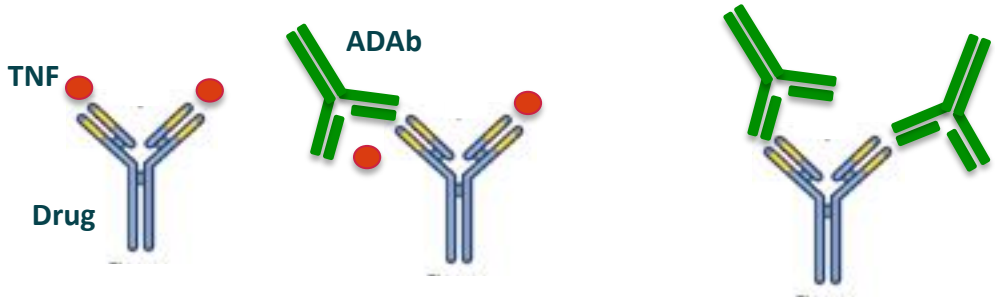
Primary Non-Responders	Secondary Non-Responders	Responders
≈ 30%	Up 70% in the first year	≈ 30%

ONE OF THE MAIN REASONS BEHIND FAILURE: DRUG IMMUNOGENICITY

Non-Responders

Biologic Phenomenon highly plausible, although with little impact near Medical Community

ANTI-DRUG ANTIBODIES (ADAb)



- ✓ Prevents antigen's neutralization (ex.TNF)
- ✓ Increases drug clearance from circulation
- ✓ May induce adverse events due to IC formation

SYSTEMATIC REVIEW AND META-ANALYSIS

Patients with RA, SpA, PsA e IBD treated with Infliximab, Adalimumab e Etanercept

Start Point: **2082** studies → 17 studies included in the MA **936 Patients**

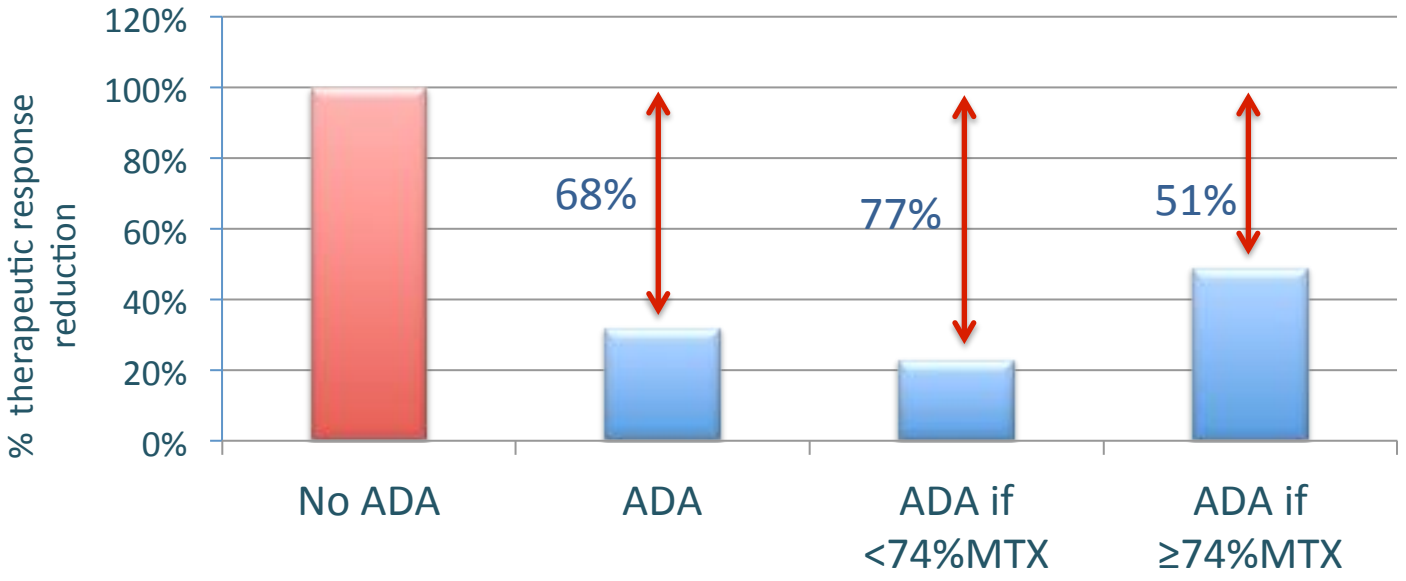
Study Objetives:

1. **The impact of ADAb on therapeutic responses**
2. **The influence of concomitant immunosuppression on ADAb detection**

Garcês S, *et al*. *Ann Rheum Dis* 2012

META-ANALYSIS - MAIN CONCLUSIONS

1 ADAb significantly reduce therapeutic effectiveness

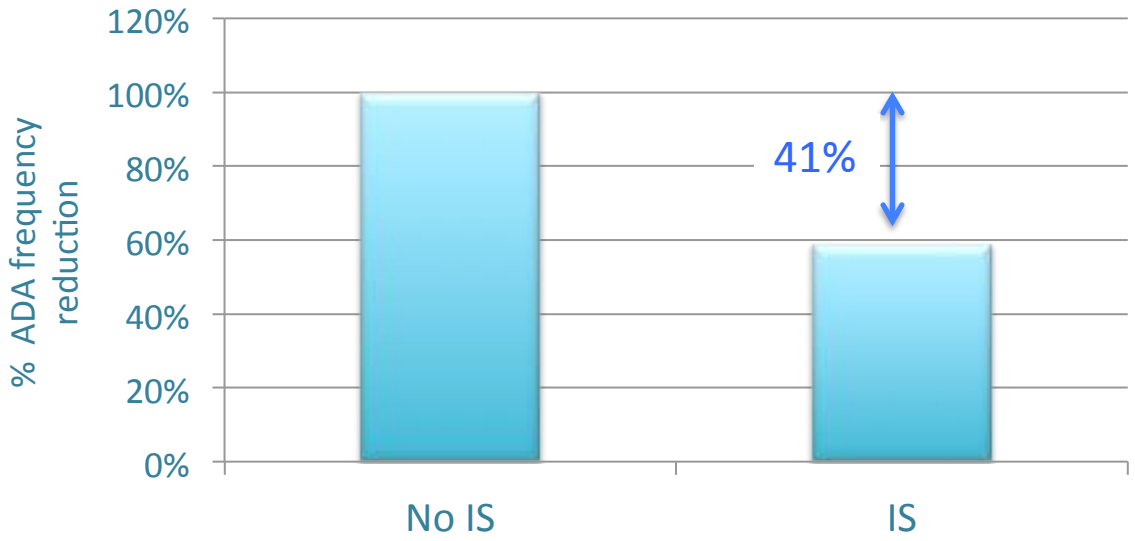


- ✓ The presence of ADAb decreased therapeutic response by 68%
- ✓ < 74% patients co-treated with MTX: the presence of ADAb decreased therapeutic response by 77%
- ✓ ≥74% patients receiving concomitant MTX: the presence of ADAb decreased therapeutic response by 51%

Garcês S, *et al*. *Ann Rheum Dis* 2012

META-ANALYSIS - MAIN CONCLUSIONS

2 Concomitant immunosuppression reduces ADAb detection



✓ Concomitant IS (MTX or AZA) decreased the detection of ADA by 41%

3 No anti-etanercept (fusion protein) Abs were detected

Garcês S, *et al*. *Ann Rheum Dis* 2012

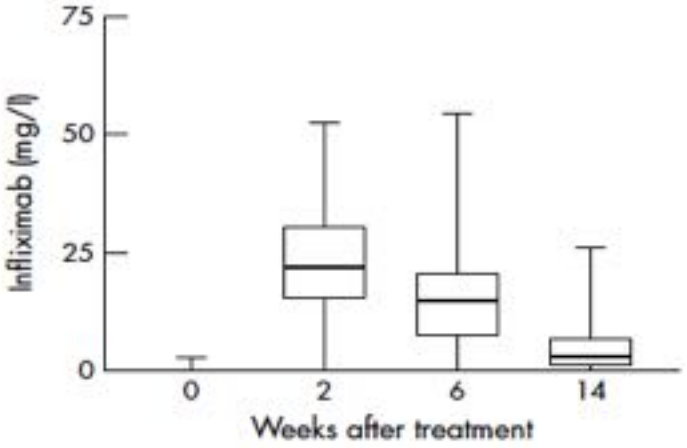
The influence of other clinical characteristics on the impact of ADAb on drug response

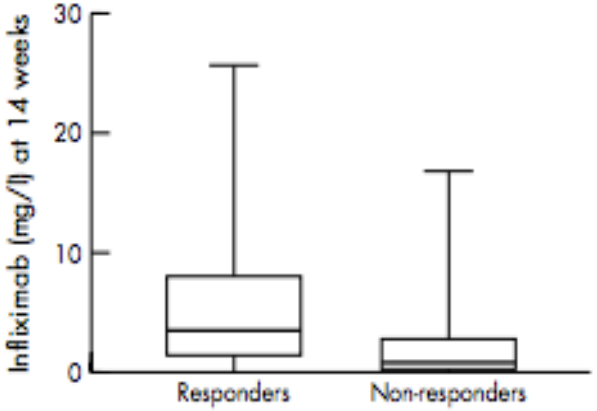
Clinical Characteristics	RR (95% CI)	P for interaction
Primary diagnosis		
RA	0.47 (0.33-0.65)	0.034
Other diseases	0.22 (0.12-0.40)	
Initiated higher biologic doses		
No	0.47 (0.33-0.65)	0.034
Yes	0.22 (0.12-0.40)	
Dose Escalation, %	0.31 (0.17-0.56)	0.57

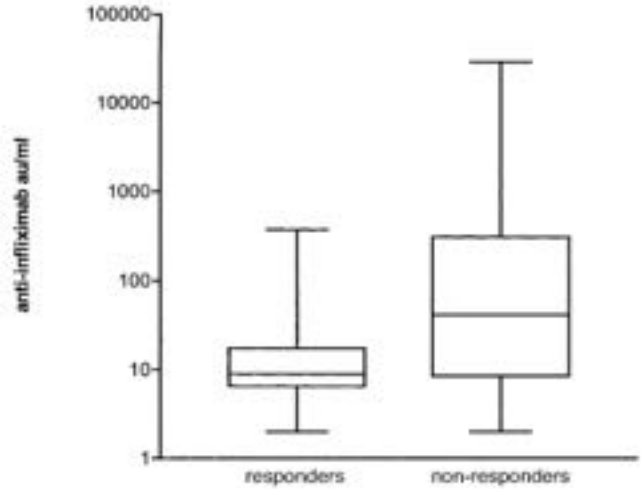
- ✓ Significant higher proportion of RA patients are receiving concomitant MTX when compared with other diseases
- ✓ Initial higher drug doses are more common in patients with other diseases (which are also less treated with MTX)

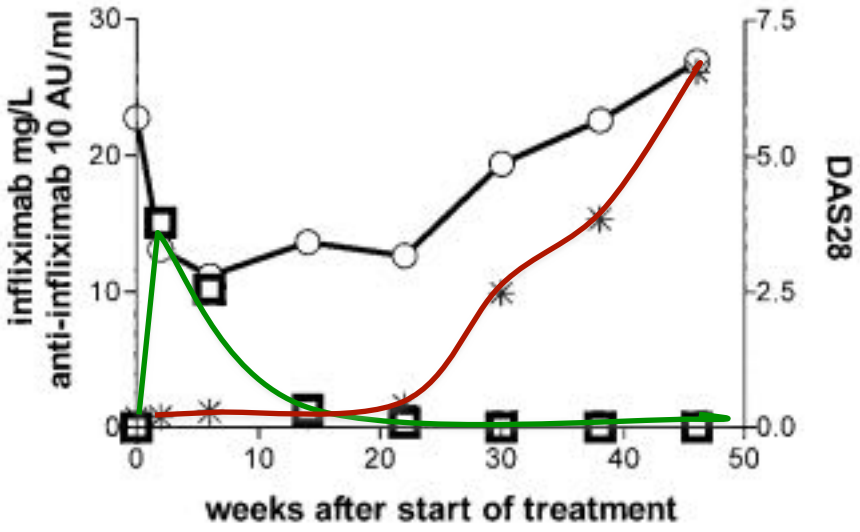
Garcês S, *et al*. *Ann Rheum Dis* 2012

ADAB REDUCE DRUG BIOAVAILABILITY



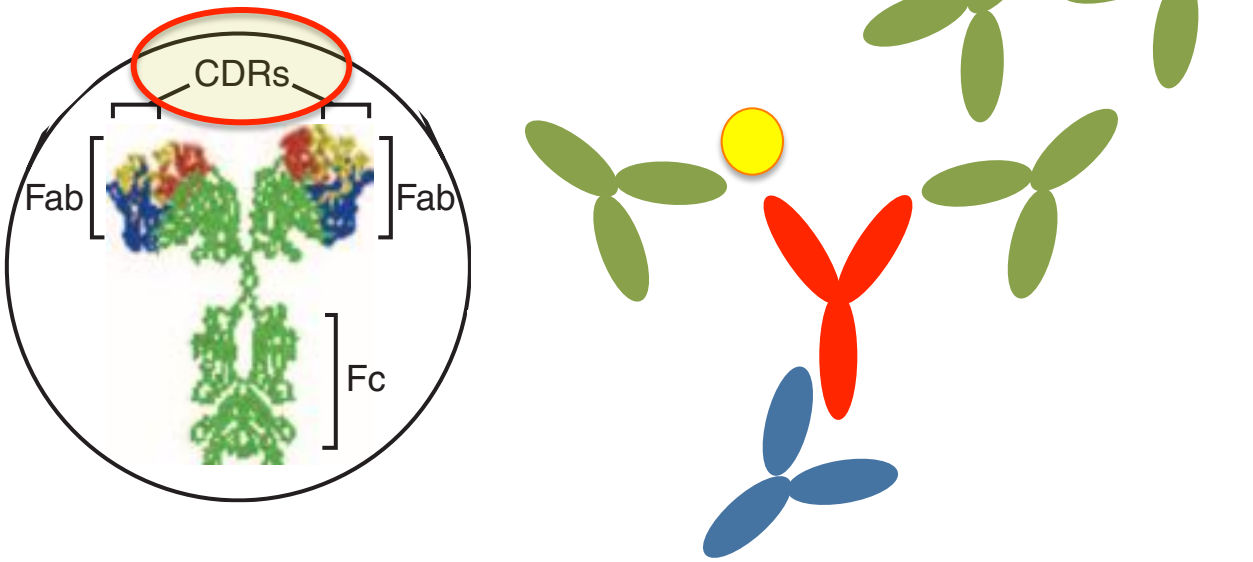






Wolbink GJ et al. Ann Rheum Dis 2005;Wolbink GJ et al. Arthritis Rheum 2006

NEUTRALIZING AND BINDING ADAB

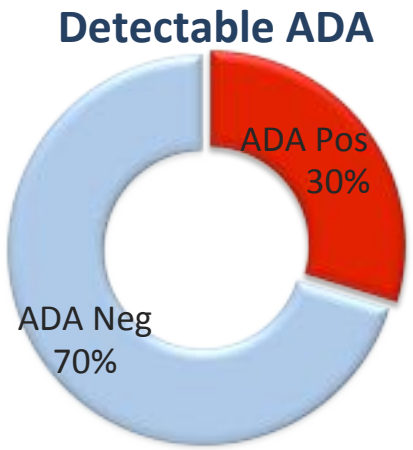


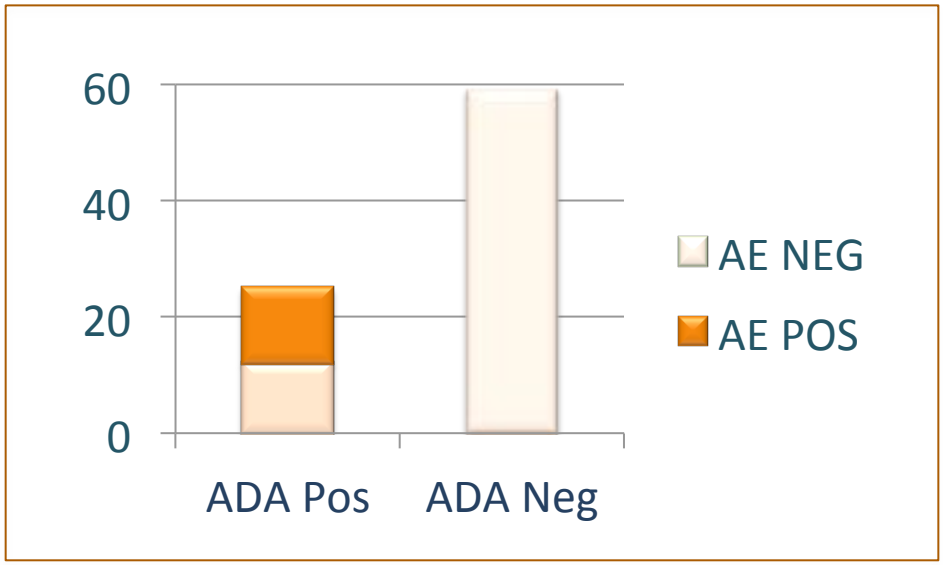
70-80% of ADAb are anti-idiotypic antibodies (IgG1 and IgG4)

Hart 2012. J Immunol Methods
Van Schouwenburg 2013. Ann Rheum Dis

ADAB IMPACT ON DRUG SAFETY PROFILE

84 patients (22 AR, 33 AS, 9 PsA, 30 IBD)
Infliximab: 3-5mg/Kg every 6-8 wks





None were able to maintain therapeutic response over time

48% of ADA-pos patients had an IrAE

Garcês S, et al. Unpublished data

CURRENT APPROACH TO PATIENTS RECEIVING BIOLOGICS

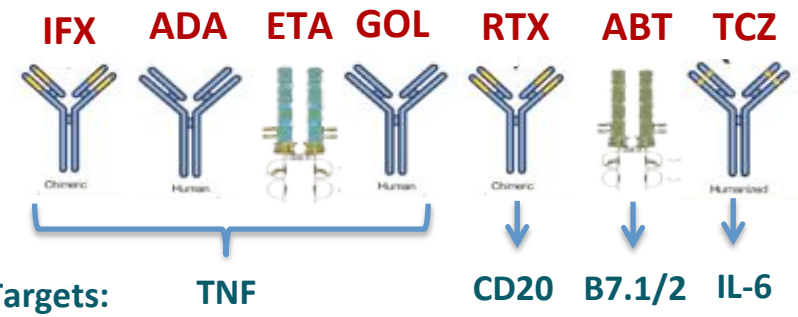
Primary Non-Responders

Secondary Non-Responders

Responders

SWITCH TO ANY OF THE APPROVED BIOLOGICS

MANTAIN THERAPY (DRUG AND DOSAGE)



CLINICAL EMPIRIC DECISION

IMPORTANT POINTS TO CONSIDER

Non-Responders

Circulating Drug Levels?

↓

Failure in the presence / absence of drug?

↓

Wrong therapeutic target?

↓

ADAb? Poor Compliance?

Responders

Circulating Drug Levels?

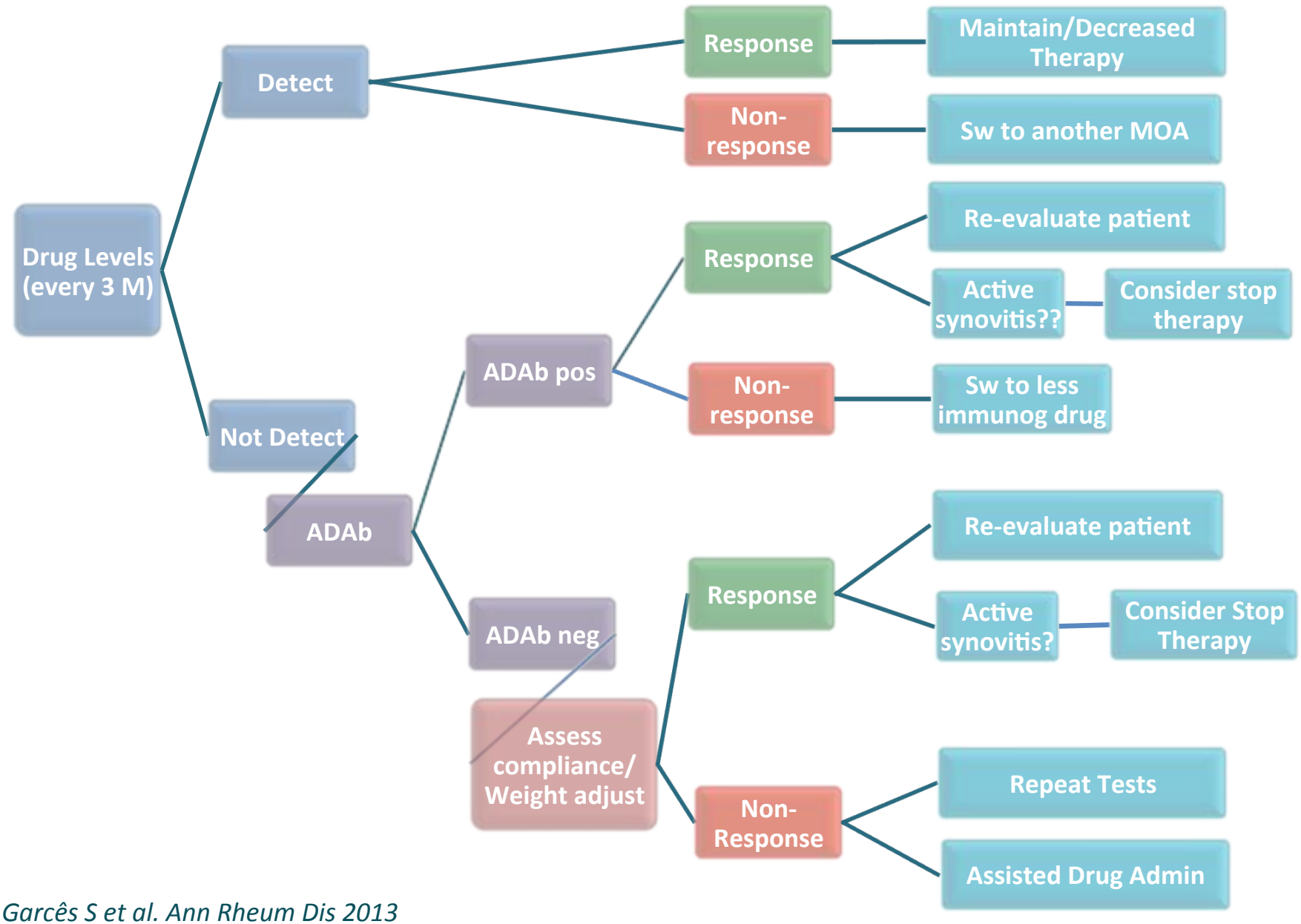
↓

High? Undetectable?

↓

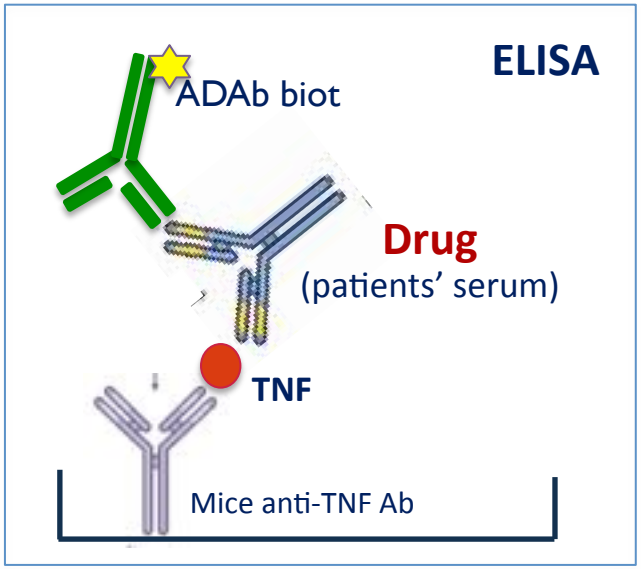
Is there a possibility to reduce or even to stop earlier in remission patients?

NEW ALGORITHM FOR PATIENTS RECEIVING BIOLOGICS

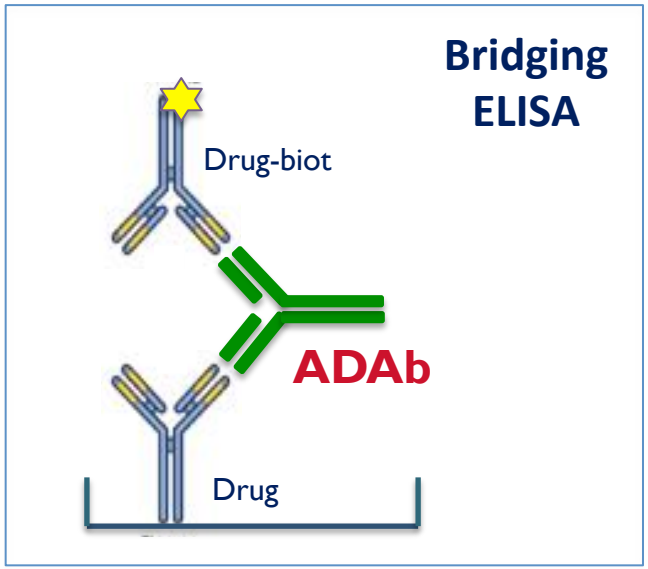


Garcês S et al. Ann Rheum Dis 2013

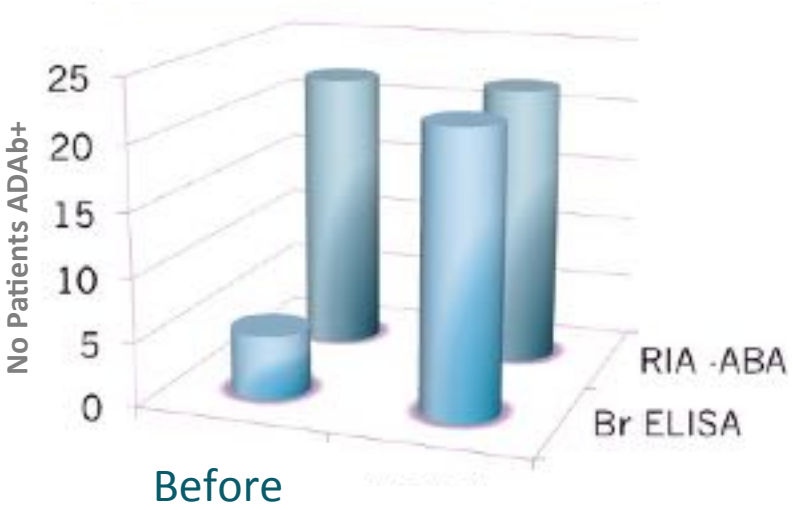
SIMPLE METHODOLOGY TO ASSESS DRUG LEVELS AND ADAB



- ✓ Without radioactivity
- ✓ Simple equipment
- ✓ Cheap method



N= 82 patients
Infliximab (3-5mg/kg 8-8wk)



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Garcês S, et al. Unpublished data

THE ALGORITHM IDENTIFIES SUBGROUPS OF PATIENTS WHO BENEFIT FROM PERSONALIZED THERAPEUTIC STRATEGIES

PREVIOUSLY PUBLISHED STUDIES THAT ALSO SUPPORT OUR ASSUMPTIONS

Non-responders

1 → **Drug +** → **Wrong Target (ex TNF vs. IL-6)** → **Sw to another MOA**

EX: Gomez-Reino et al. Ann Rheum Dis 2012

Multicenter Spanish Study
Follow up 3 yrs
1124 pts with failure to 1 aTNF

- 533 Sw to aTNF
- 591 Sw to RTX

**(free of significant immunogenicity, i.e., we expect detectable drug levels during the entire interval between drug administrations)*

Failure to Etanercept*

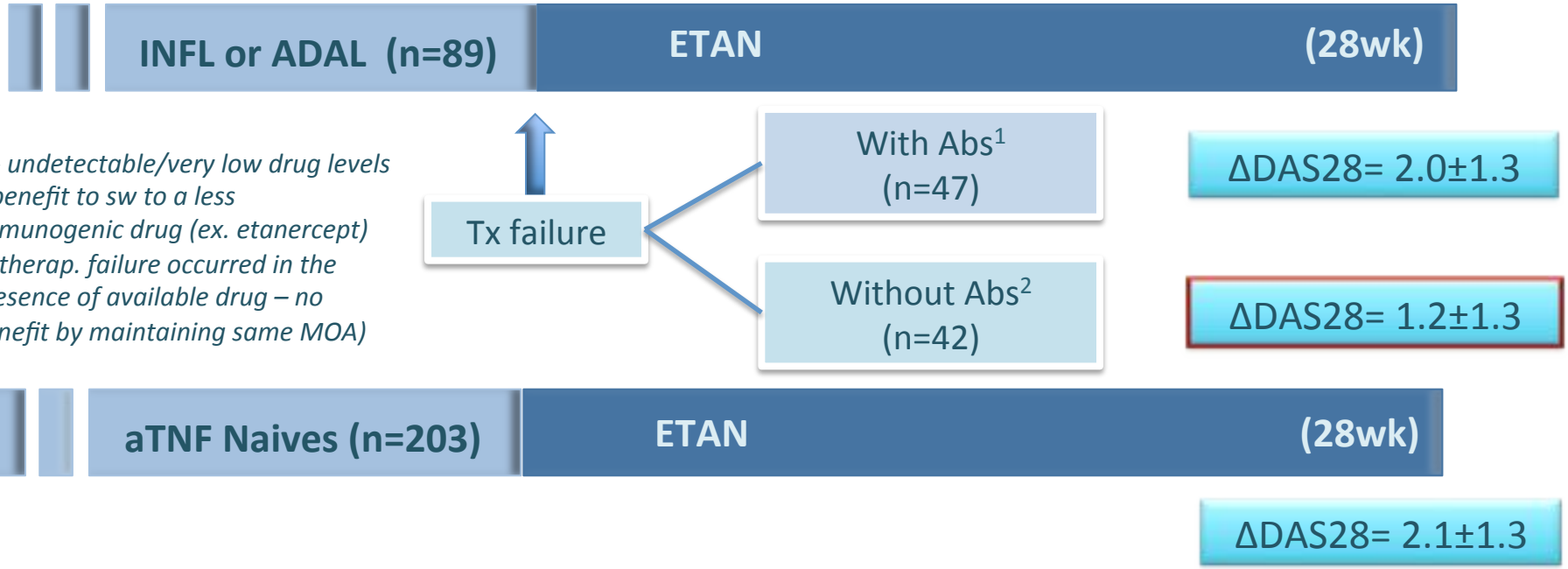
	Rituximab		Adalimumab/infliximab		
DAS28	Mean (SD)	N†	Mean (SD)	N†	p Value*
6 months	−1.61 (1.56)	221	−1.04 (1.33)	143	0.001
9 months	−1.35 (1.54)	78	−1.39 (1.48)	72	0.36
12 months	−1.81 (1.60)	121	−1.55 (1.49)	104	0.05

PREVIOUSLY PUBLISHED STUDIES ALSO SUPPORT OUR ASSUMPTIONS

Non-responders

1	Drug +	→	Wrong Target (ex TNF vs. IL-6)	→ Sw to another MOA
2	Drug -	→	ADAb +	→ Sw to less immunogenic drug

EX: Jamnitski A. Ann Rheum Dis 2011, 68:531-5



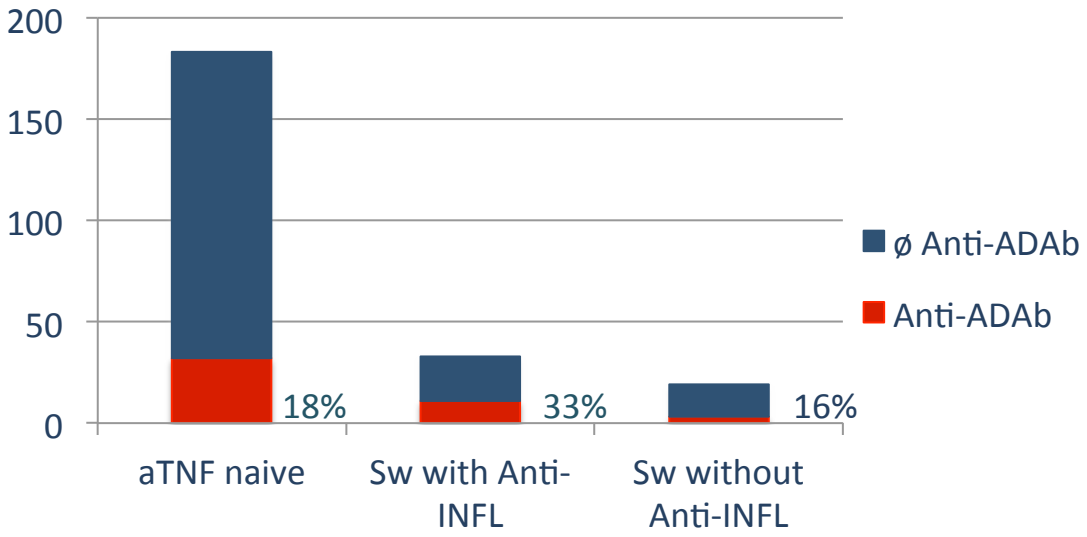
PREVIOUSLY PUBLISHED STUDIES ALSO SUPPORT OUR ASSUMPTIONS

Non-responders

2 | **Drug -** → **ADAb +** → **Sw to less immunogenic drug**

EX: Bartelds GM et al. Ann Rheum Dis 2010

Patients who produce ADAb against one biologic have ≈2-fold higher probability to produce ADAb against the another one



WHAT CAN WE CONSIDER AS A LESS IMMUNOGENIC DRUG?

- ✓ **Not fully elucidated >>> Lack of comparative data using the same assays**
- ✓ **But… Important evidence already exists:**

1. No neutralizing ADAb have been described to Soluble Receptors (etanercept and abatacept)

2. By using the same type of assays:

- around 50% of INF-treated patients develop ADAb within first year-treatment
- around 30% of ADAL-treated patients develop ADAb within first year-treatment

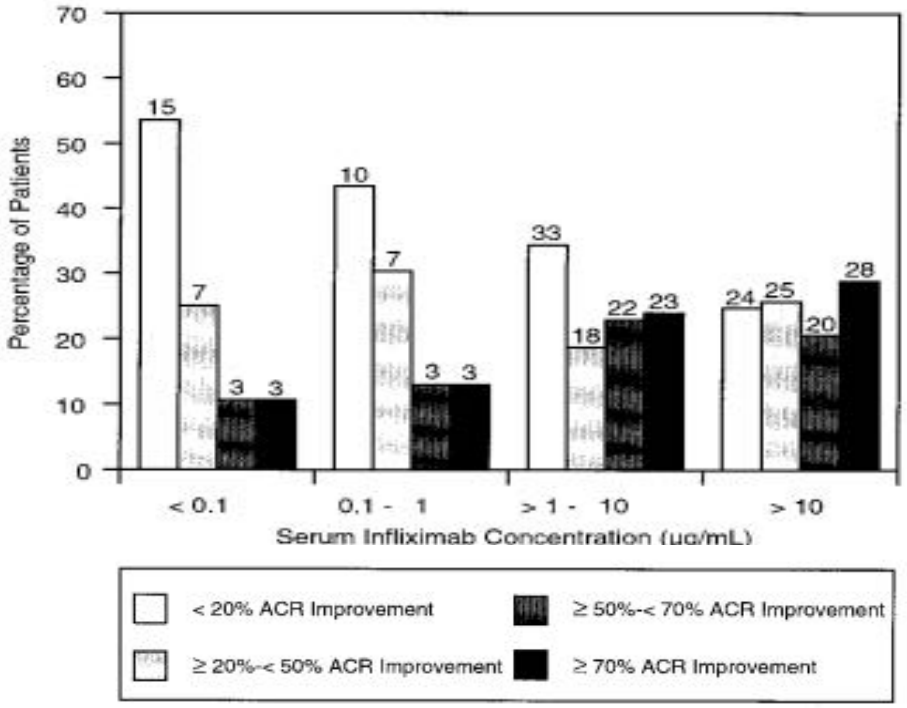
Garcês S et al. Ann Rheum Dis 2012
Garcês S et al. Ann Rheum Dis 2013
Bartelds GM et al. Ann Rheum Dis 2010
Bartelds GM et al. JAMA 2011
Pascual-Salcedo et al. Rheumatology 2011

PREVIOUSLY PUBLISHED STUDIES ALSO SUPPORT OUR ASSUMPTIONS

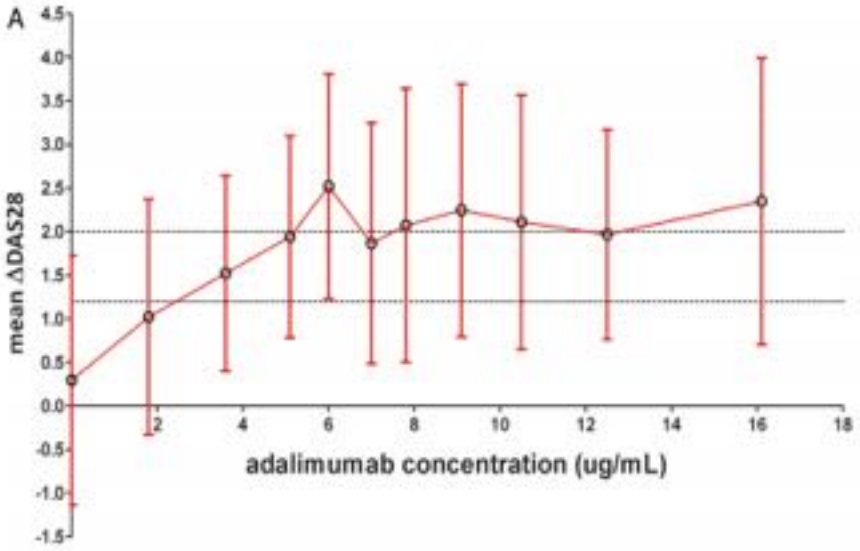
Responders

3 | **Drug +** → **Consider progressive drug reduction**

EX: St Clair et al. Ann Rheum Dis 2002 – ATTRACT study
Pouw et al. Ann Rheum Dis 2013



> 1ug/mL infliximab >> no significant difference in effectiveness



> 5ug/mL adalimumab >> no significant difference in effectiveness

PREVIOUSLY PUBLISHED STUDIES ALSO SUPPORT OUR ASSUMPTIONS

Responders

4 **Drug -** → **If remission, consider stop therapy**

EX: van der Maas et al. BMC Musculoskeletal Disorders 2012

Table 2 Percentage of low and high infliximab serum trough levels and presence of anti-infliximab antibodies in patients with low and high DAS28 at the first study visit

	No infliximab serum trough level	Low* infliximab trough levels	Intermediate infliximab trough levels	High** infliximab trough levels	Anti-infliximab antibodies	Total
DAS28	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)	N° patients
<2.6	13 (2–23)	23 (10–35)	48 (32–63)	18 (6–29)	13 (2–23)	40
≤3.2	13 (4–20)	18 (9–28)	55 (43–67)	14 (5–22)	11 (3–19)	65
>3.2	29 (19–39)	18 (10–27)	32 (22–42)	21 (12–30)	29 (19–39)	82

* Low serum trough levels are defined as <1.0 mg/L.
** High serum trough levels are defined as >5.0 mg/L.

Remission – 66% have infliximab levels above 1 ug/mL

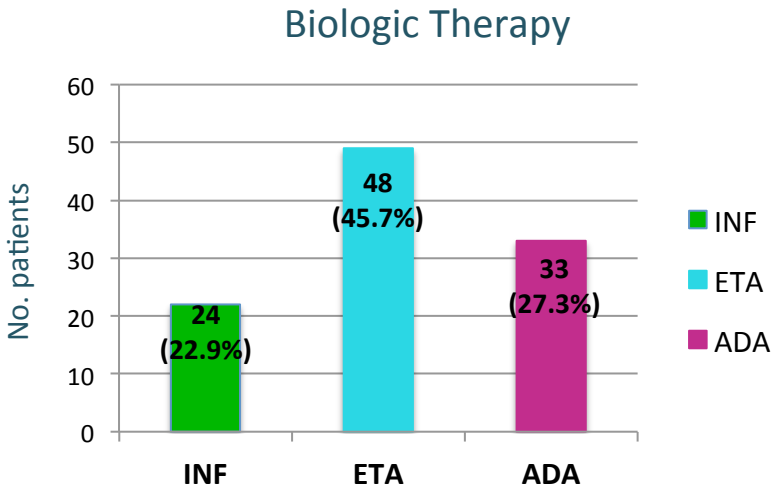
OUR ALGORITHM'S PERFORMANCE IN CLINICAL PRACTICE

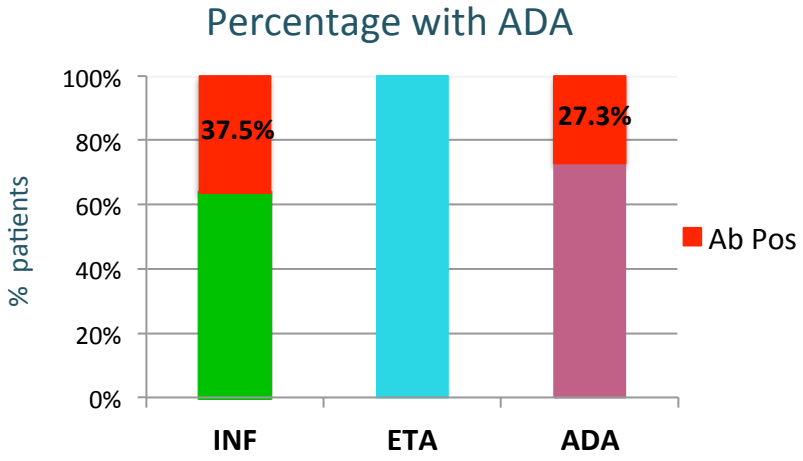
Model: RA patients starting by TNFi

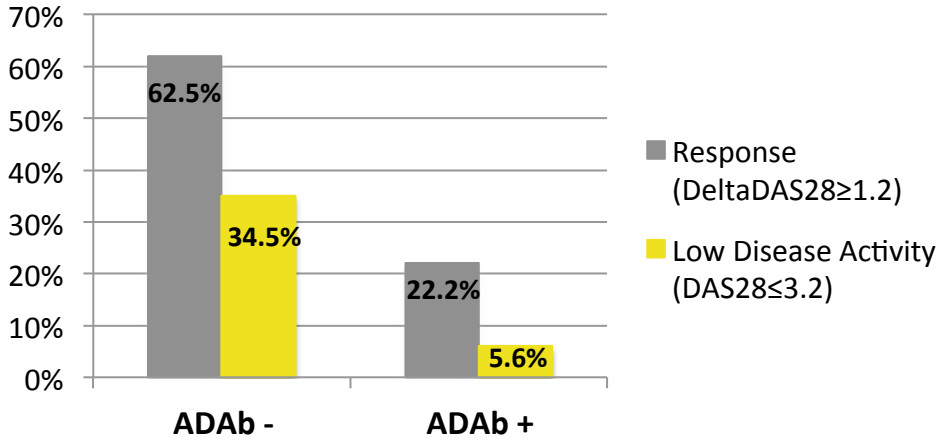
- 105 RA patients
- Therapy: Infliximab, Adalimumab, Etanercept
- Follow-Up: 2 years (Fev 2010-Jan 2012)
- Drug levels and ADAb assessed at every 3 Mo
- Clinicians blind for the tests' results

Objectives:

1) Concordance grade between current approach and our proposed algorithm
2) Clinical outcomes between concordant and non-concordant therapeutic strategies with the algorithm







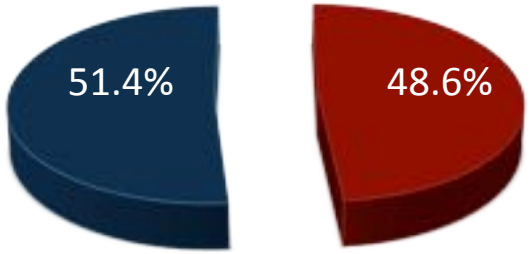
All ADAb+ patients had undetectable drug levels
All ADAb- have detectable drug levels

Garcês S et al. Ann Rheum Dis 2013

OUR ALGORITHM'S PERFORMANCE IN CLINICAL PRACTICE

Model: RA patients starting by TNFi

1 Concordance Grade with the New AlgoritHm



DELAY
249 days (≈ 8 Mo)

2 New Algorithm: 10 x Higher Probability of Low Disease Activity

	Group A (N=54)	Group B (N=51)	P value
Response	88%	49%	$p<0.001$
	OR= 7.91 (3.27-19.3)		
Low Disease Activity	69%	19%	$p<0.001$
	OR=9.77 (4.69-20.37)		

Over one year after therapeutic decision

Garcês S et al. Ann Rheum Dis 2013

ROUTINE IMMUNOGENICITY ASSESSMENT WILL ALLOW US TO DO:

1- Faster switches to other biologics

2- Better switches to other biologics, by choosing the appropriate one

MORE COST-EFFECTIVE THERAPEUTIC STRATEGIES

BEYOND THE ALGORITHM

Mechanisms Underlying Immunogenicity

- **Patient-related factors favoring/controlling ADAb response**
  - Genetic / Immunological factors - Prediction of immunogenicity
  - Type of disease
  - Concomitant therapies
    - Mechanism underlying the modulation of immunogenicity by MTX

- **Drug-related factors favoring/controlling ADAb response**
  - Induction dosages (initial higher doses and immune tolerance)
  - The influence of drug's mechanism of action on ADAb responses

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PATIENTS

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