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XXX CONGRESSO NAZIONALE
SIAAIC
Società Italiana di Allergologia,
Asma ed Immunologia Clinica

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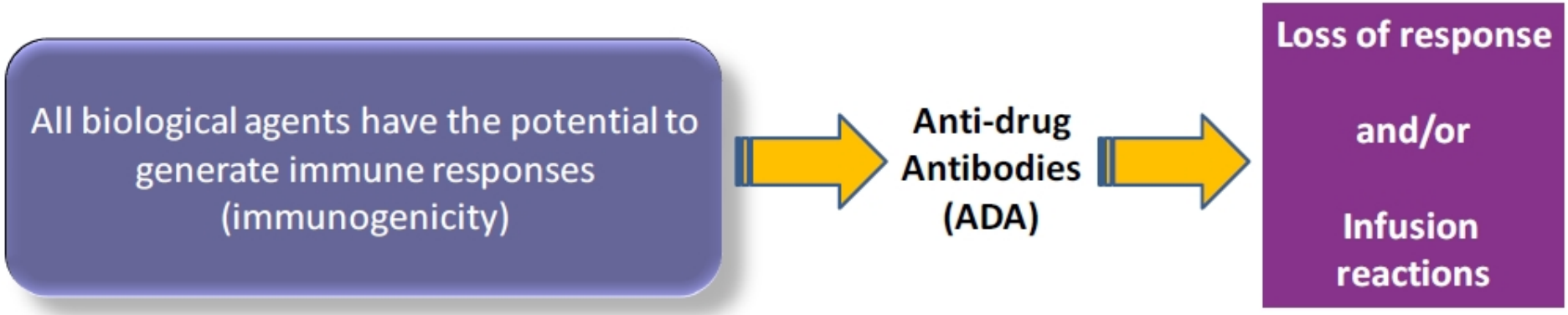
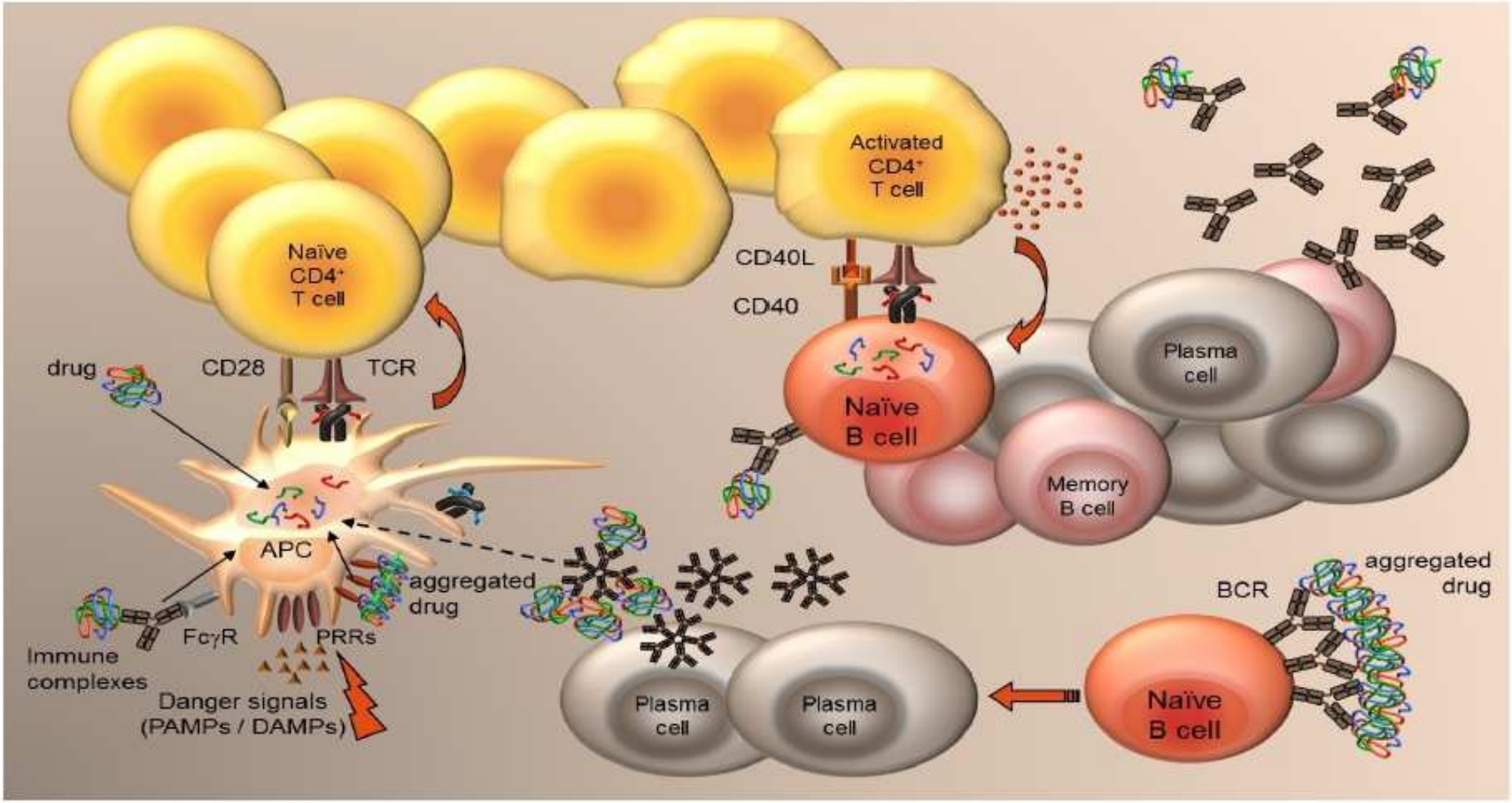
IMMUNOGENICITA' DEI FARMACI BIOLOGICI

IMMUNOGENICITY: definition

- "Unwanted" **immunogenicity** consists of the response that the immune system displays towards biological agents

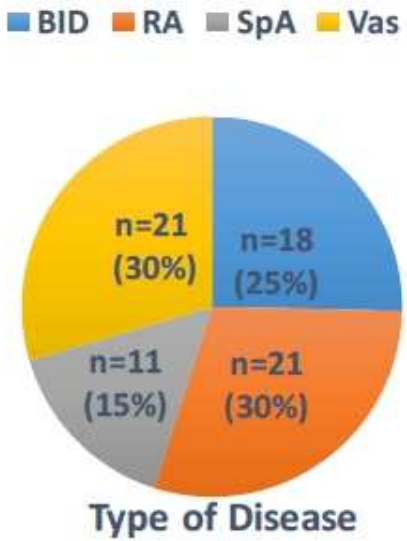


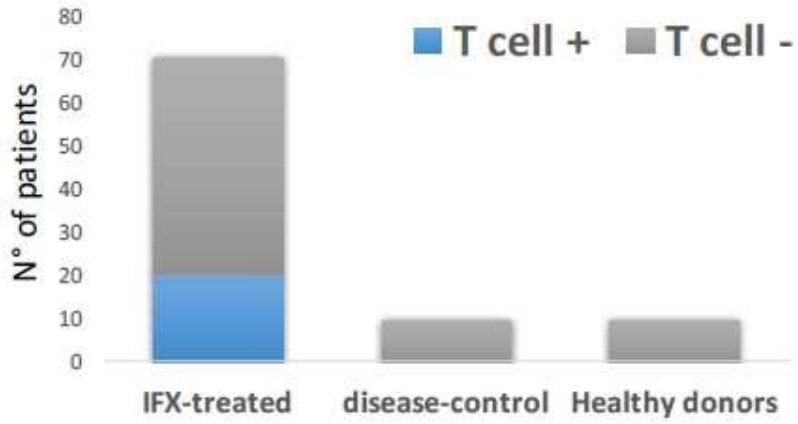
IMMUNE RESPONSE TO BIOLOGICALS



T CELL RESPONSE TO INFLIXIMAB IN EXPOSED PATIENTS

71 IFX-exposed patients, 10 untreated disease control patients, 10 healthy donors (cocolture DC/CD4+ T cells)





(Vultaggio A et al, Clin Exp Immunol 2016)

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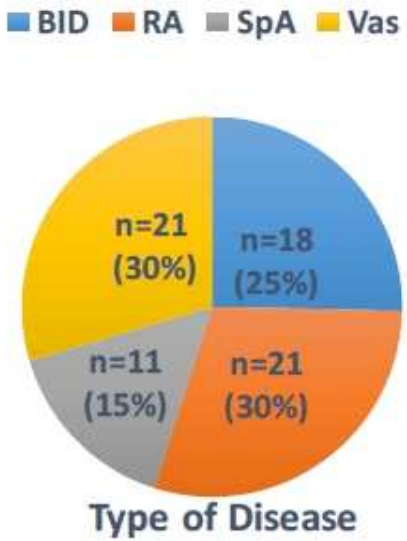
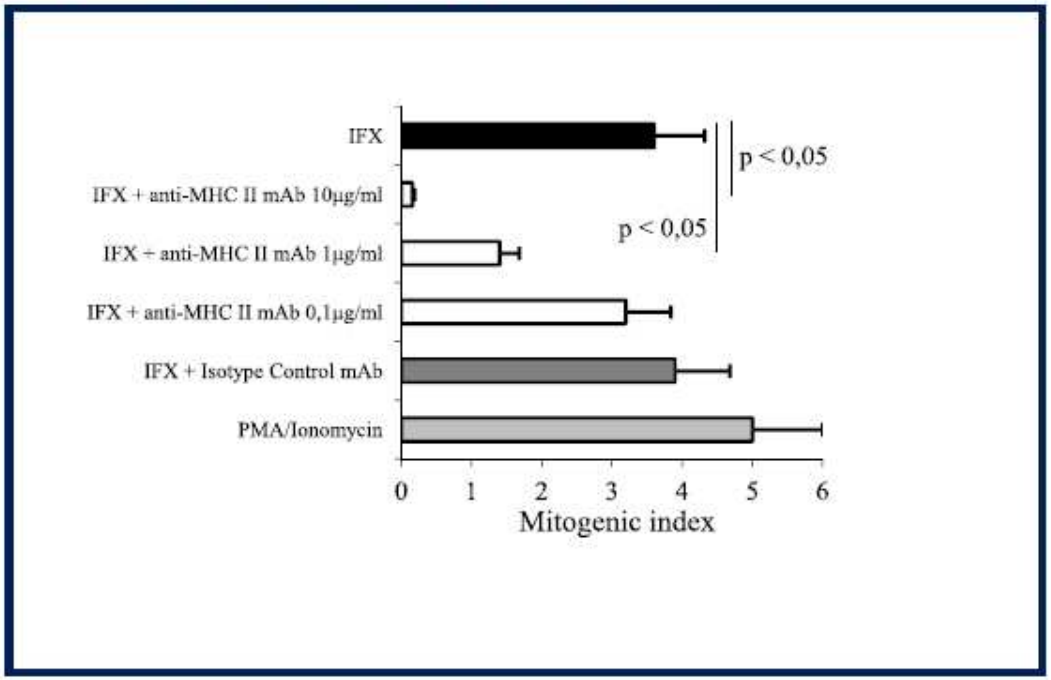


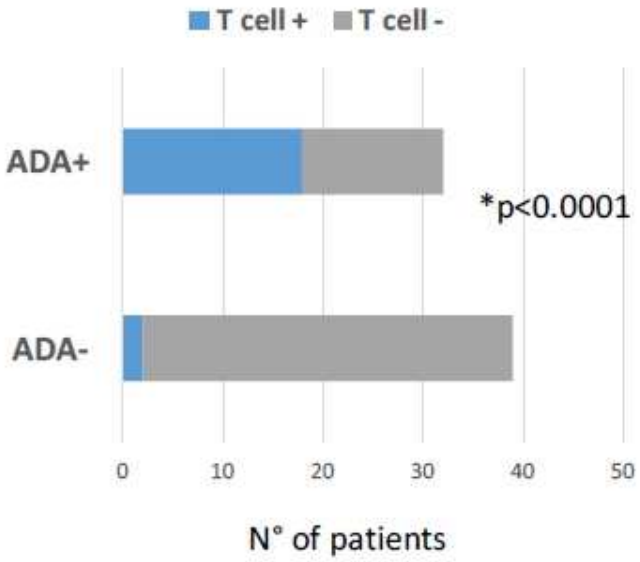


(Vultaggio A et al, Clin Exp Immunol 2016)

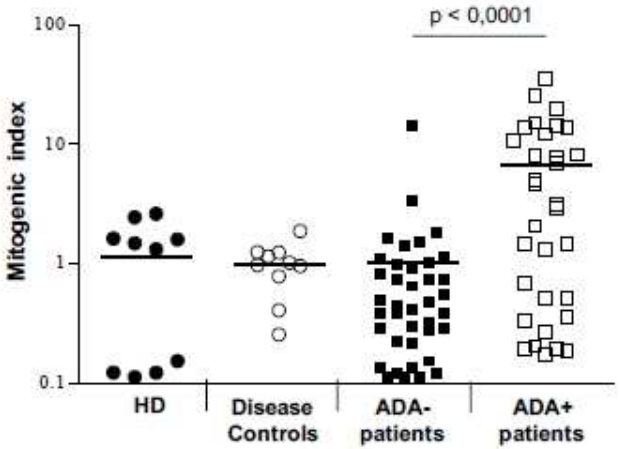
T CELL RESPONSE: correlation with ADA status (1)

ADA status
N=39 ADA-
N=32 ADA+

A significantly higher proportion of T cell positivity developed among **ADA+ patients (56.6%)** than in **ADA- patients (5.1%)**



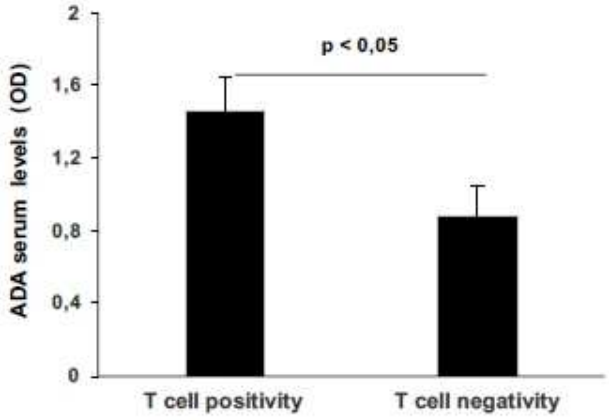
A stronger T cell positivity is detectable in **ADA+ patients** than in **ADA- patients** as suggested by MI mean values



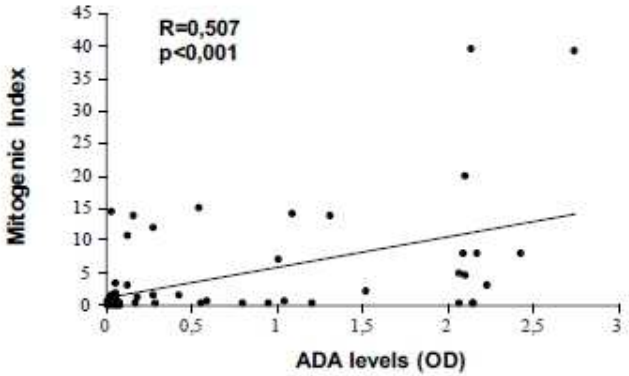
(Vultaggio A et al, Clin Exp Immunol 2016)

T CELL RESPONSE: correlation with ADA status (2)

Patients with T cell positivity display significantly higher ADA serum levels



A direct and significant correlation exists between degree of T cell response and ADA serum levels

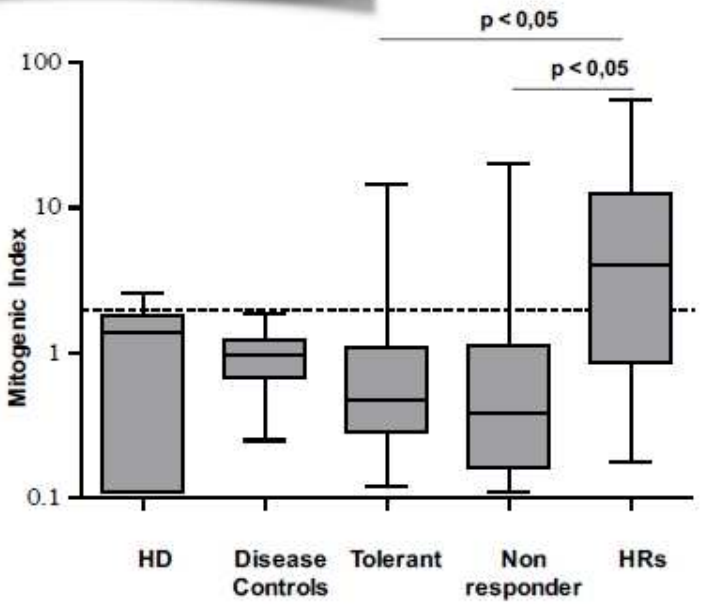


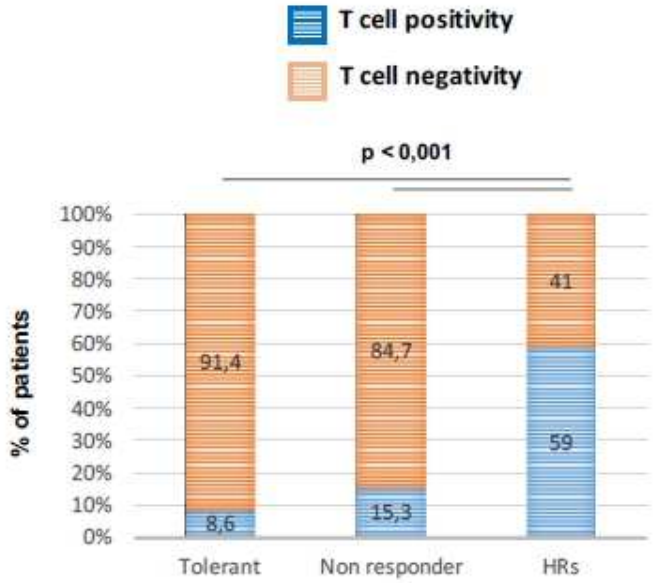
(Vultaggio A et al, Clin Exp Immunol 2016)

IMMUNOGENICITY AND CLINICAL OUTCOME TO THE TREATMENT

Clinical outcome:
Tolerant = 23
Non responder= 26
Reactive = 22

Cellular response correlates with hypersensitivity reactions

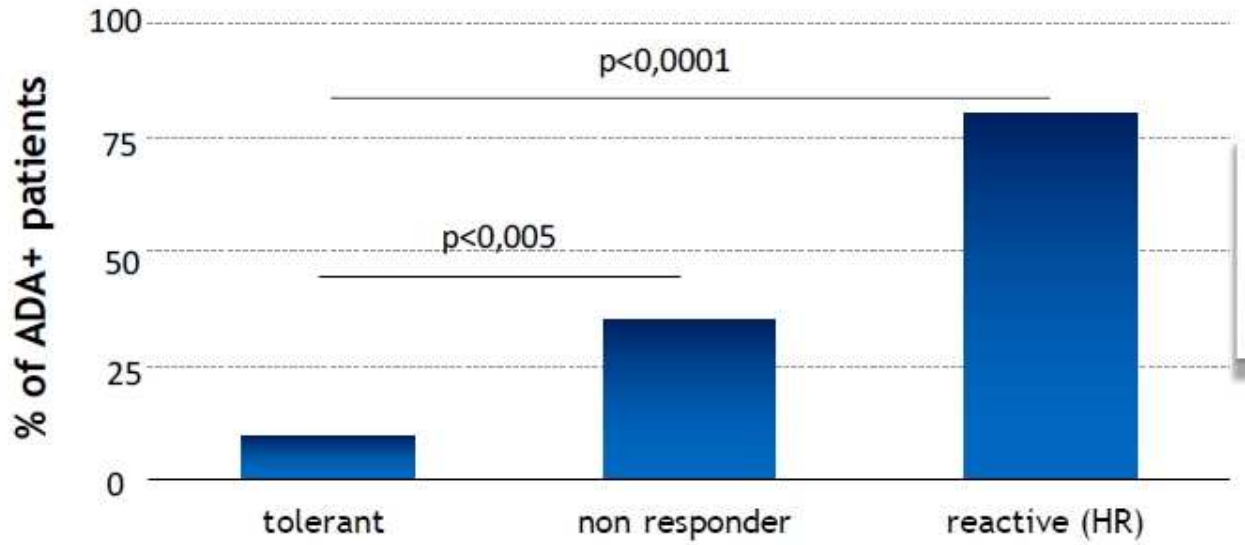




(Vultaggio A et al, Clin Exp Immunol 2016)

IMMUNOGENICITY AND CLINICAL OUTCOME TO THE TREATMENT

Humoral response correlates with hypersensitivity reactions and loss of response



346 Infliximab-treated patients

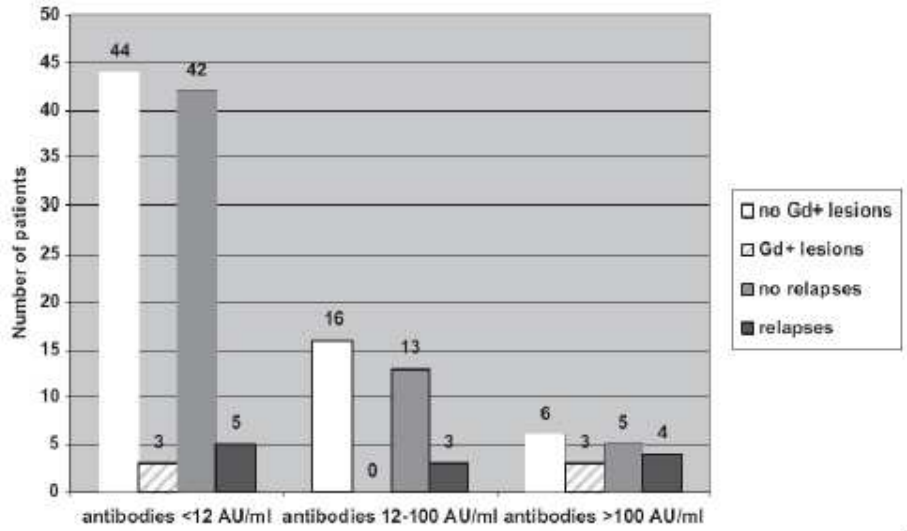
Tolerant n=200
Non responder n=93
Reactive n=53

About 45% resulted ADA+

(personal unpublished data)

IMMUNOGENICITY of (other) BIOLOGICALS: clinical impact

Clinical relevance of serum natalizumab concentration and anti-natalizumab antibodies in multiple sclerosis



(Vennegoor A et al, Mult Scler 2013)

ADA: heterogenous in composition

A mixture of different quantities of different:

- **Isotypes (IgG, IgA, IgM, IgE)**
- **Affinities (low, high)**
- **Specificities (idiotype, allotype, glycans)**

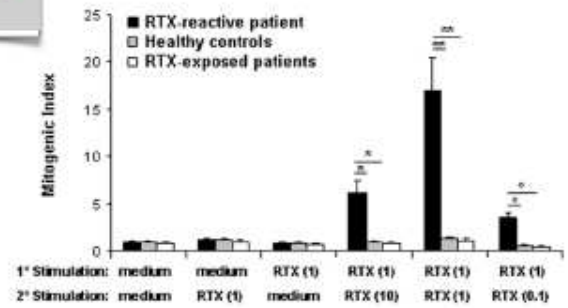
1. **No all patients develop ADA**
2. **No all ADA+ patients develop ADA-related events**
3. **No all ADA+ patients develop the same ADA-related event**

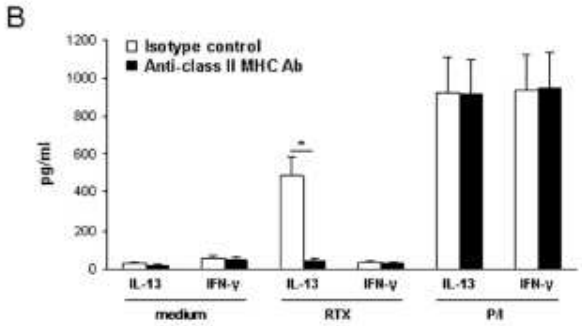
(Rup B et al, Clin Exp Immunol 2015)

CYTOKINE PROFILE OF IFX-SPECIFIC T CELLS AND ADA ISOTYPE

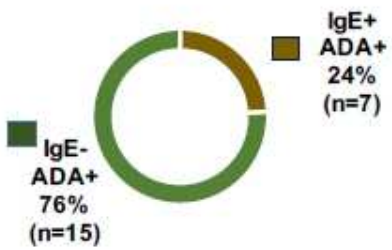
RITUXIMAB

1 HR patient IgE+

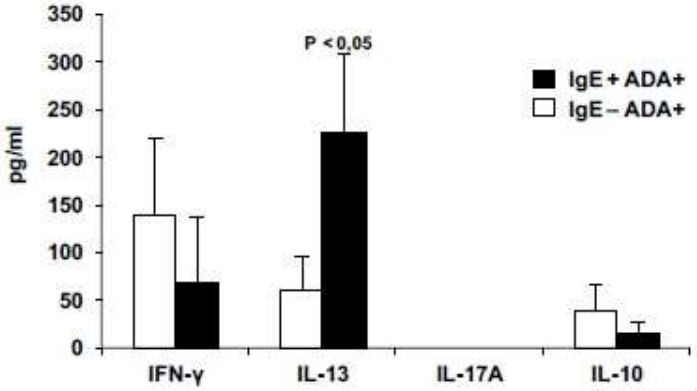




HRs patients (n=22)



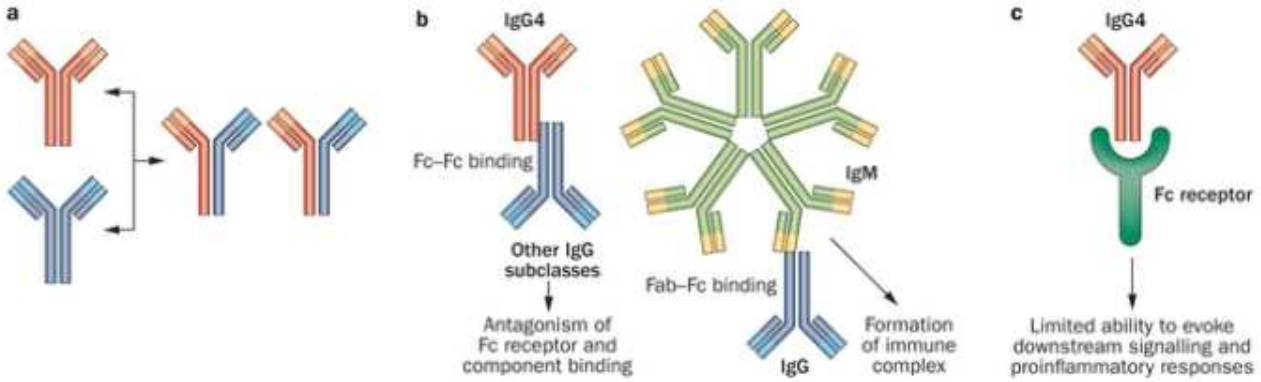
INFLIXIMAB



(Vultaggio A et al, IAAI 2012)

(Vultaggio A et al, Clin Exp Immunol 2016)

IgG4 SUBCLASS: an unusual antibody



- **Fab-Arm Exchange** ……→ monovalency……→ **…undetectable with ELISA bridging assay**
- **Lack of cross-linking activity** ……→ ….formation of small immune complexes
- **Poor trigger of complement**
- **Low affinity to activating Fc receptors**

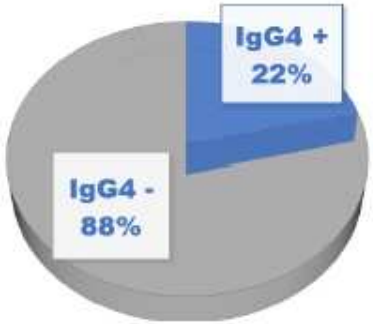
IgG4 are considered "blocking antibodies"

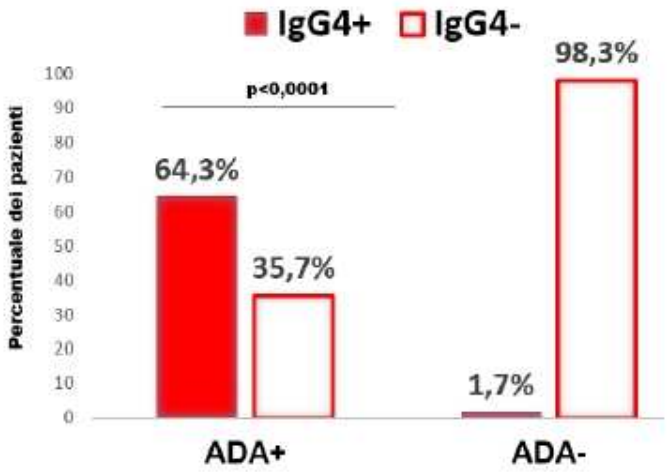
ANTI-INFLIXIMAB IgG4 ANTIBODIES

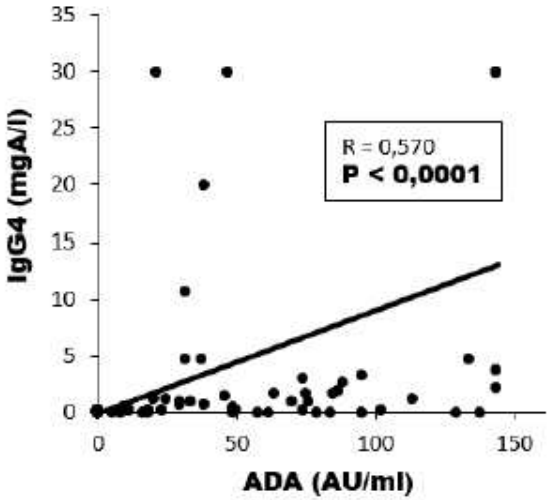
ASSAY: Modified IFX-coated ImmunoCAP provided by Phadia (Uppsala, Sweden)

ImmunoCAP

172 IFX-treated patients with different immuno-mediated diseases

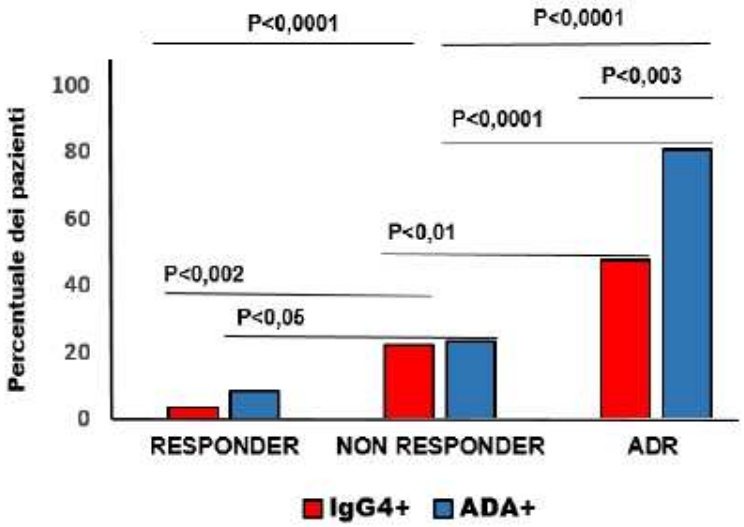


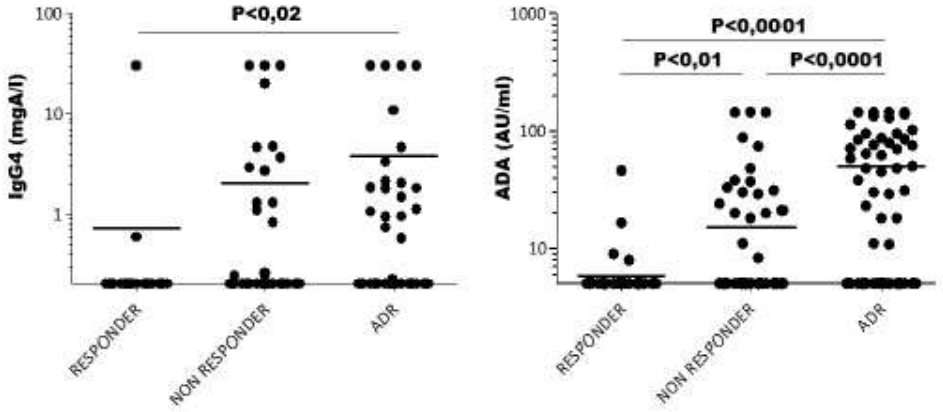




(manuscript in preparation)

ANTI-INFLIXIMAB IgG4 ANTIBODIES IN REACTIVE PATIENTS (hypersensitivity reactions)

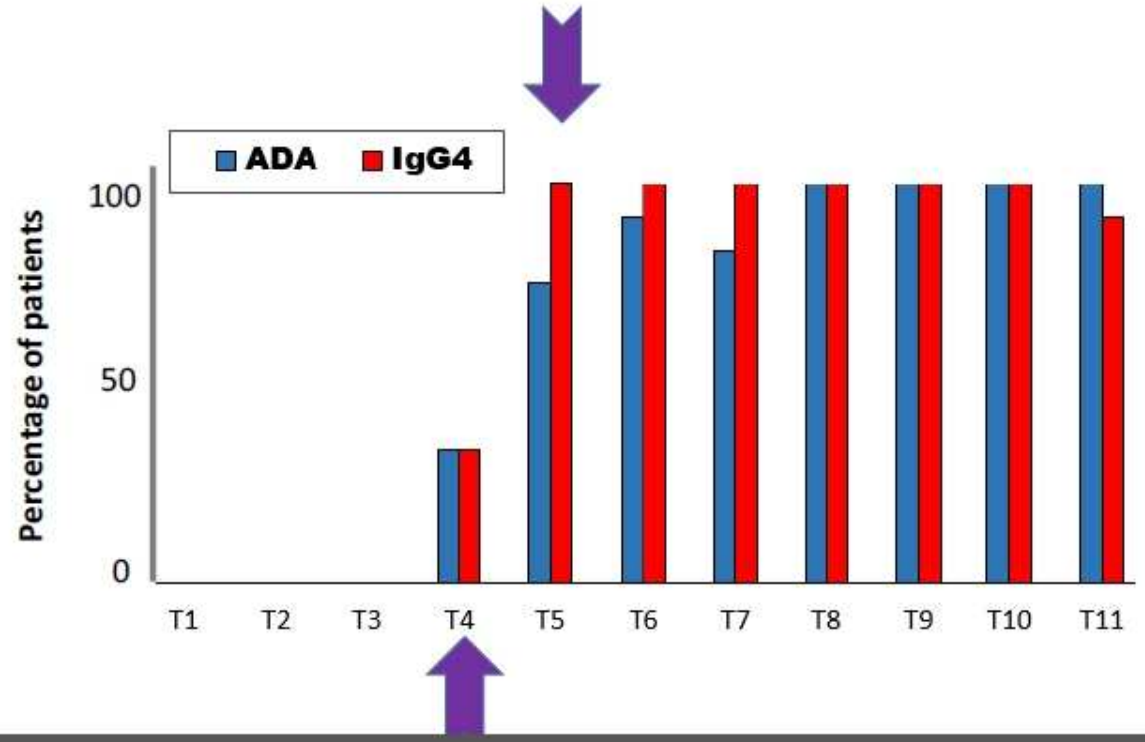




(manuscript in preparation)

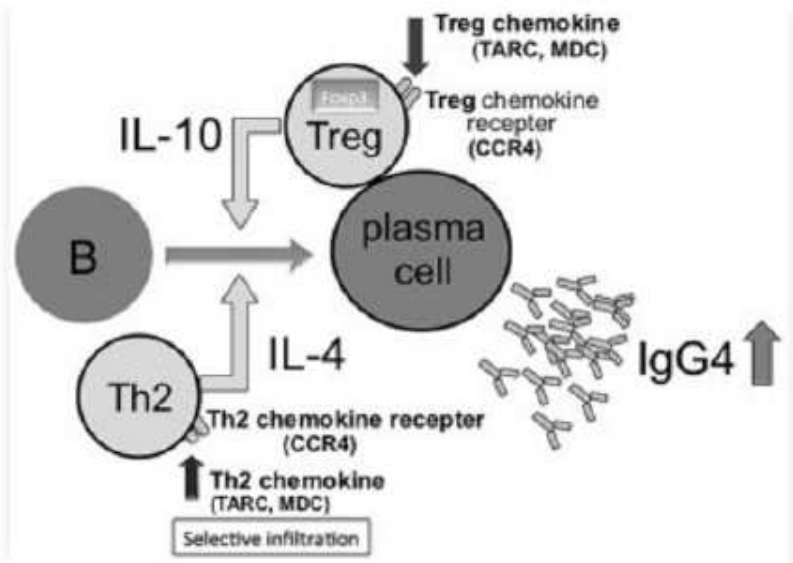
EARLY ONSET OF ANTI-INFLIXIMAB IgG4 ANTIBODIES

14 IFX-treated patients longitudinally monitored



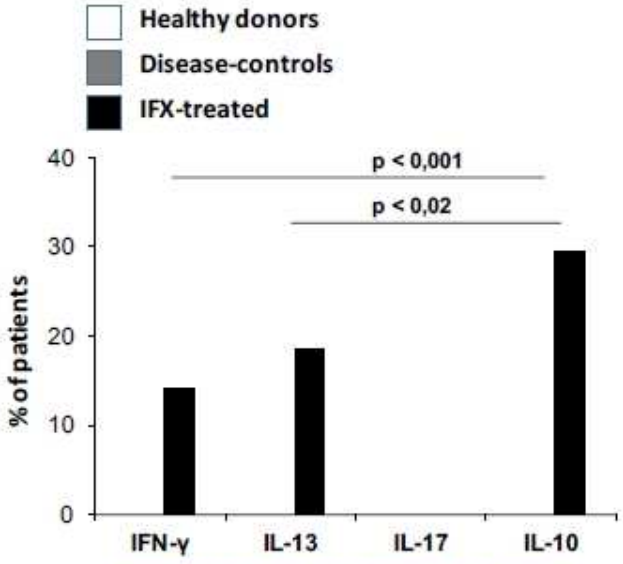
(manuscript in preparation)

ROLE OF IL-10 IN IgG4 DEVELOPMENT



Tanaka, A. *et al.* Th2 and regulatory immune reactions contribute to IgG4 production and the initiation of Mikulicz disease. *Arthritis Rheum.* **64**, 254–263 (2012)

IFX-driven IL-10 production



IL-10 was the most frequently detected cytokines (29.5% of patients)

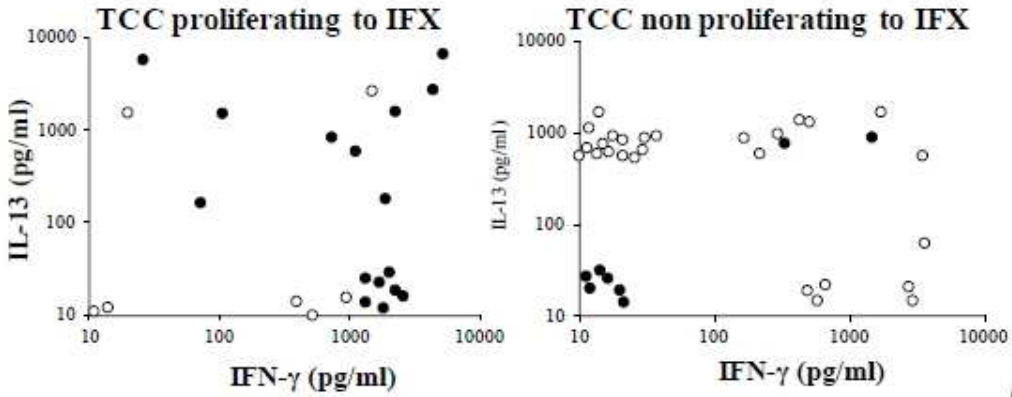
(Vultaggio A et al, Clin Exp Immunol 2016)

T CELL INVOLVEMENT IN IFX-INDUCED IL-10 PRODUCTION

IFX-specific T cell clone (TCC) were generated (from 1 ADA+ patient)

Total TCC	188
Clonal Efficiency*	24.5%
TCC CD4+ CD8-	156 (83%)
TCC CD8+ CD4-	28 (14.9%)
TCC γδ CD4- CD8-	4 (2.1%)
TCC CD4+CD39+CD73+	13 (7%)
IFX-Specific TCC:	58 (29,8%)
Proliferating TCC	23 (12.2%)
Non proliferating cytokine-producing TCC	35 (18.6%)

● IL-10 producing TCC



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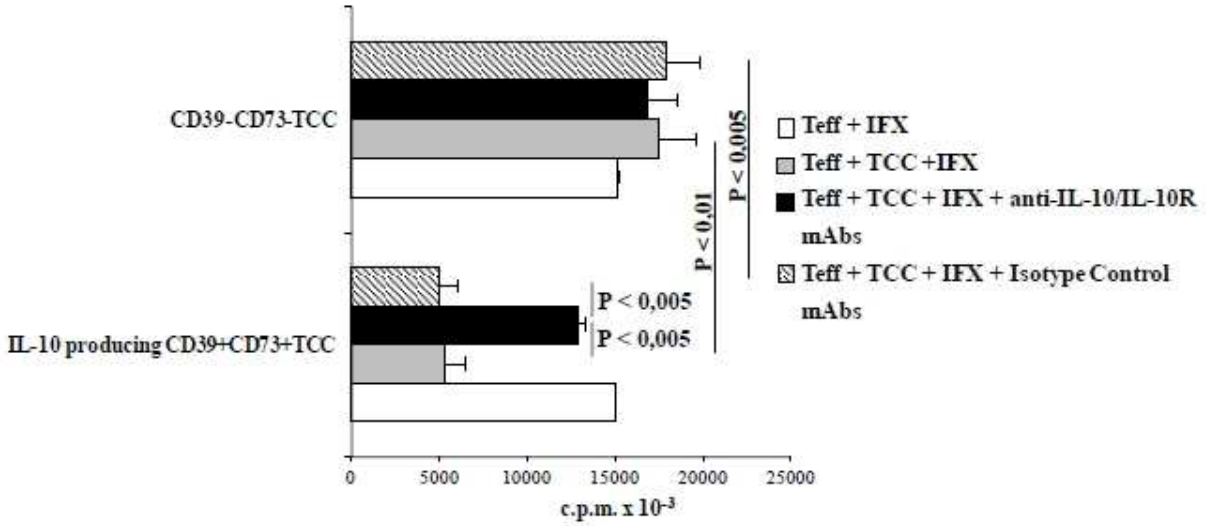
IFX-INDUCED IL-10 IS FUNCTIONALLY ACTIVE (in vitro)

IL-10 producing T regulatory clones inhibit effector T cell clones



(manuscript submitted)

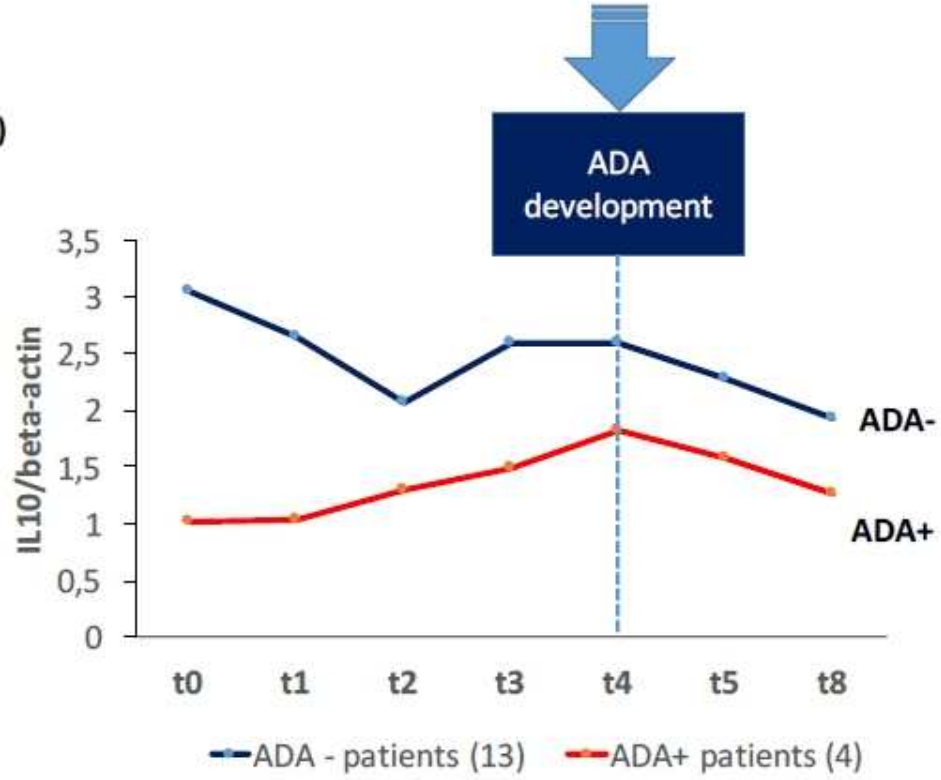
IS IFX-INDUCED IL-10 FUNCTIONALLY ACTIVE IN VIVO?

- 17 Patients enrolled before the beginning of treatment (IFX)
- they have been monitoring during the first 8 infusions

(up to now, the n of infusions ranges from 3 to 8)*

- Methods:
  1. cytokine (IL-10, IFN-g, IL-13, IL-17) mRNA expression In PBMCs upon in vitro re-stimulation with IFX (24h)
  2. ADA assessment
  3. Clinical outcome monitoring

- 4 patients developed ADA (all after the 4th infusion)
- 3 patients displayd immunogenicity-related events (LOR and ADR)
- 1 patient w/o events

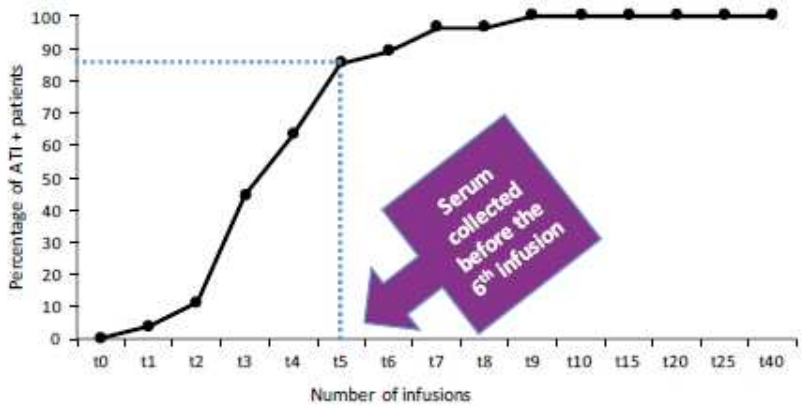


(Personal Unpublished data)

MONITORING ADA DEVELOPMENT: our experience

From 2007 to 2015, 79 IFX-treated patients were monitored* for ADA development and clinical outcome *[about 1200 serum samples evaluated]*

* Serum collected before each infusion



- 46.8 % of IFX-treated patients developed ADA,
- Among ADA+ patients, the large majority of them (85%) developed ADA within the first 5 infusions (about 6 months)

(personal unpublished data)

ADA DEVELOPMENT: prediction of clinical outcome

Anti-drug antibodies

ORIGINAL ARTICLE

The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease

Niels Vande Casteele,[1,2,3] Reena Khanna,[3] Barrett G Levesque,[2,3] Larry Stitt,[3] G V Zou,[3] Sharat Singh,[4] Steve Lockton,[4] Scott Hauenstein,[4] Linda Ohrmund,[4] Gordon R Greenberg,[5] Paul J Rutgeerts,[6] Ann Gils,[1] William J Sandborn,[2] Séverine Vermeire,[6] Brian G Feagan[3]

454 patients

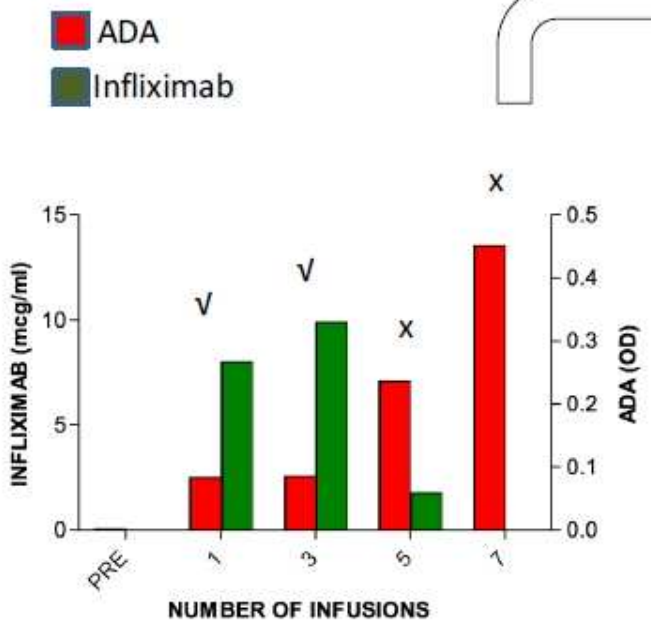
ATI (anti-infliximab antibodies) presence in "current" sample is a independet predictor for the presence of C-Reactive Protein >5 mg/L (surrogate of disease activity) in a "future" sample *(p<0.006)*

Δ time between "current" and "future" sample: 56 ± 14 days

(Vande Casteele N et al GUT 2015)

IS ADA POSITIVITY PREDICTIVE FOR THE CLINICAL OUTCOME?

Pz with Psoriasic arthritis + Crohn Disease IFX-treated



The 8th infusion was complicated by an immediate reactions characterized by **itching, flushing, dyspnea**

Stop therapy and rescue treatment

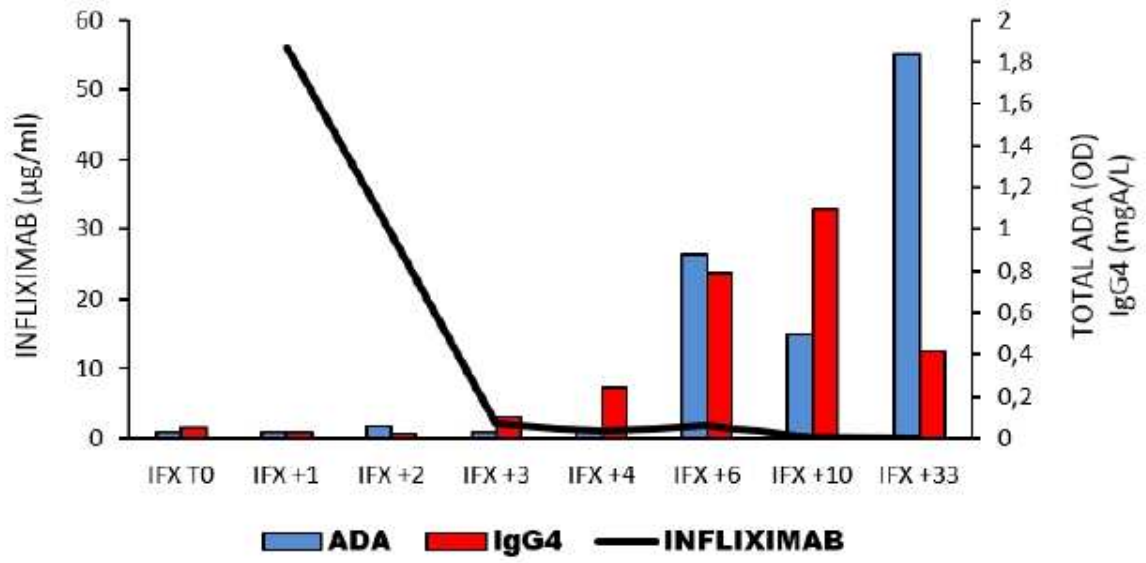
10 days later
erythema and edema of the right thigh appeared

Power Doppler ecography: **thrombosis of saphena**

Thrombophilia and other coagulation pathway alterations were ruled-out

(Personal unpublished data)

TROUGH LEVELS OF IFX ARE PREDICTIVE FOR ADA DEVELOPMENT



(Personal Unpublished data)

IMMUNOGENICITY AND BIOSIMILARS

IBD patients

Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima

Shomron Ben-Horin,[1] Miri Yavzori,[1] Itai Benhar,[2] Ella Fudim,[1] Orit Picard,[1] Bella Ungar,[1] SooYoung Lee,[3] SungHwan Kim,[3] Rami Eliakim,[1] Yehuda Chowers[4]

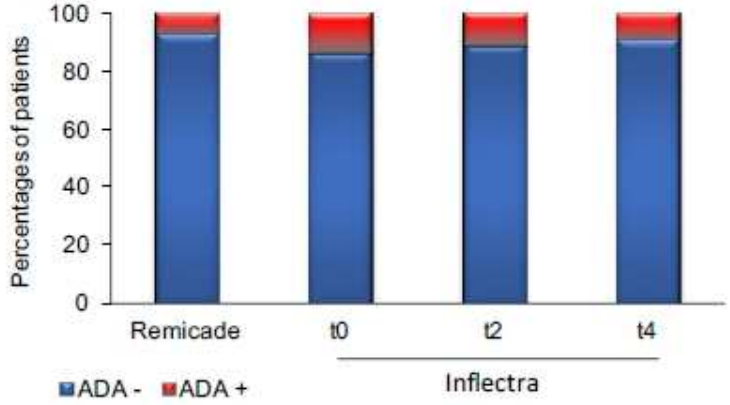
RA patients

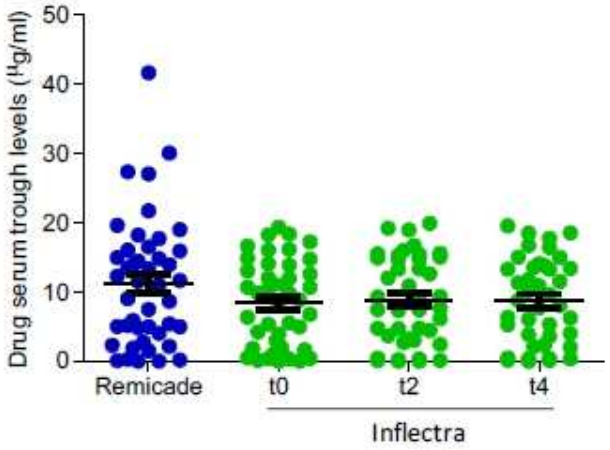
Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars

M Begoña Ruiz-Argüello,[1] Ainara Maguregui,[1] Ainhoa Ruiz del Agua,[1] Dora Pascual-Salcedo,[2] Ana Martínez-Feito,[3] Teresa Jurado,[4] Chamaida Plasencia,[4] Alejandro Balsa,[4] Francisca Llinares-Tello,[5] José Rosas,[6] Nerea Torres,[1] Antonio Martínez,[1] Daniel Nagore[1]

IMMUNOGENICITY of IFX-BIOSIMILAR in PEDIATRIC IBD PATIENTS

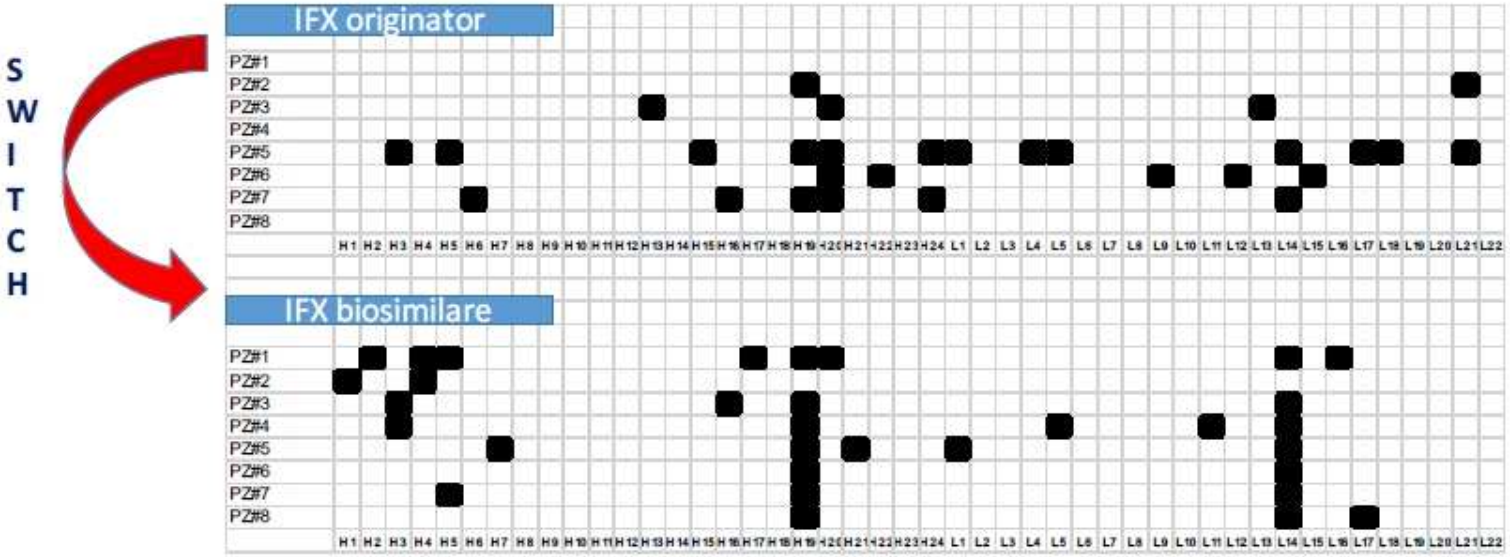
44 pediatric patients:
7 Ulcerative Colitis
37 Crohn disease





(manuscript in preparation)

IMMUNOGENICITY of IFX-BIOSIMILAR: Cellular response to drug peptides



(Personal unpublished data)

FINAL REMARKS

- Both humoral and cellular immune responses are involved in the immunogenicity of biologicals
- Development of the immune response appears as a potential problem in current practice
- Immunogenicity of biological agents has to be taken into account in the management of treated patients

.....The final chapter of this is story is not written.....

(Wendling D e al, 2017)

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Lennart Venemalm