KATHOLIEKE UNIVERSITEIT
LEUVEN

Optimising anti-TNF treatment on the basis of trough levels and anti-drug antibodies

Niels Vande Casteele
Laboratory for Pharmaceutical Biology

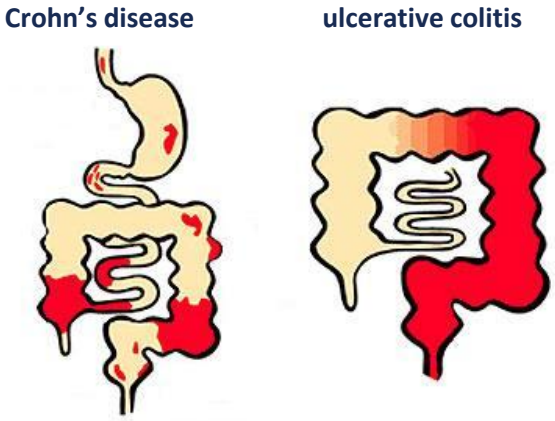
Confidential

Copenhagen, February 8th 2012, EIP

General introduction: pathology and therapy

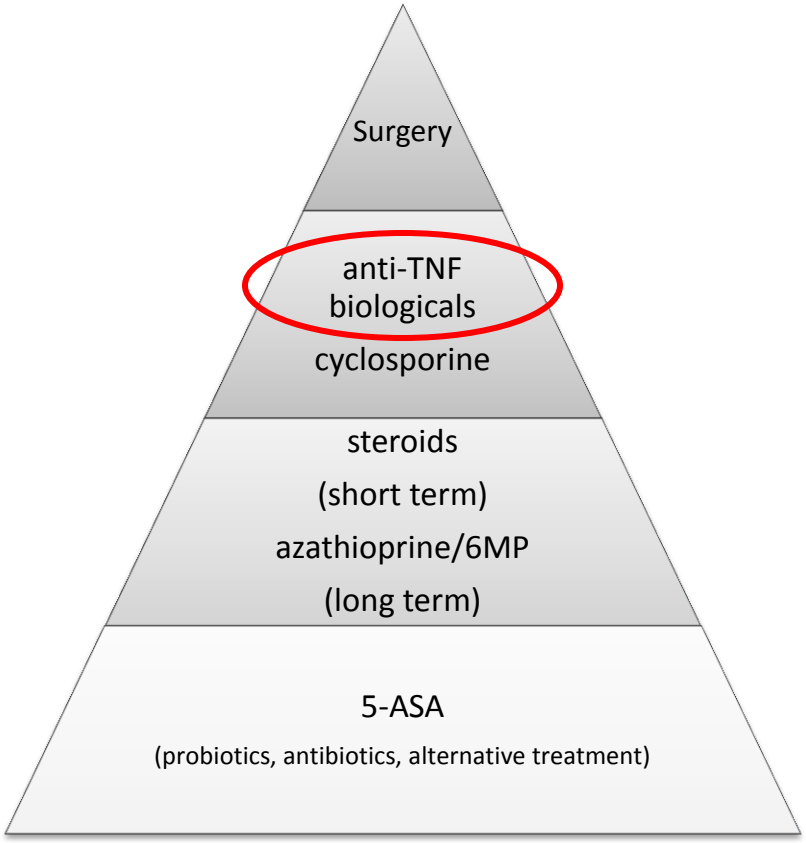
Inflammatory Bowel Disease (IBD)

- Relapsing inflammation of the intestine characterised by flares and remission.



- Crohn's disease (CD) = transmural disease
- Ulcerative colitis (UC)= mucosal disease

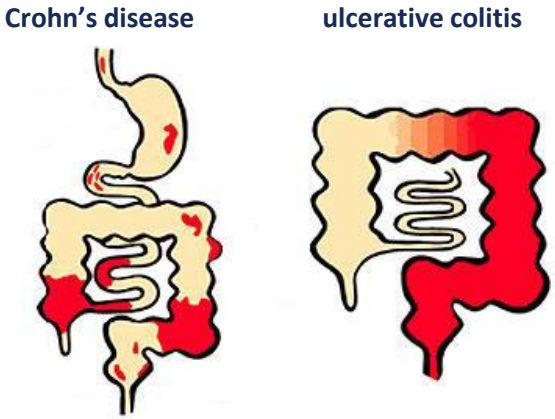
Treatment



General introduction: pathology and therapy

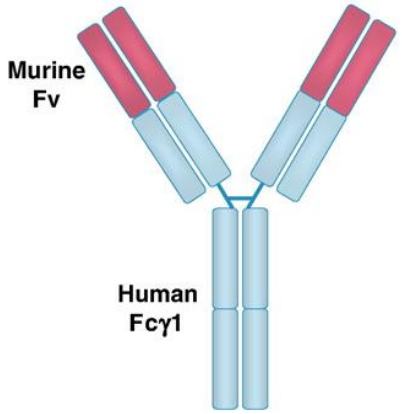
Inflammatory Bowel Disease (IBD)

- Relapsing inflammation of the intestine characterised by flares and remission.

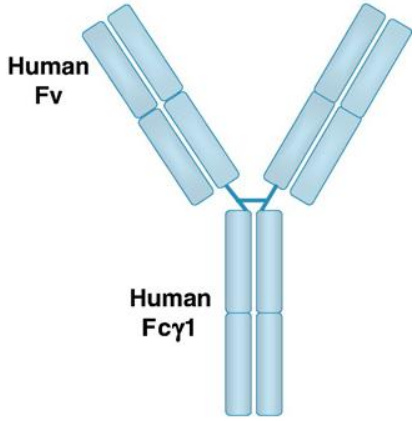


- Crohn's disease (CD) = transmural disease
- Ulcerative colitis (UC)= mucosal disease

Anti-TNF biopharmaceuticals



Remicade®
infliximab
(75% human)



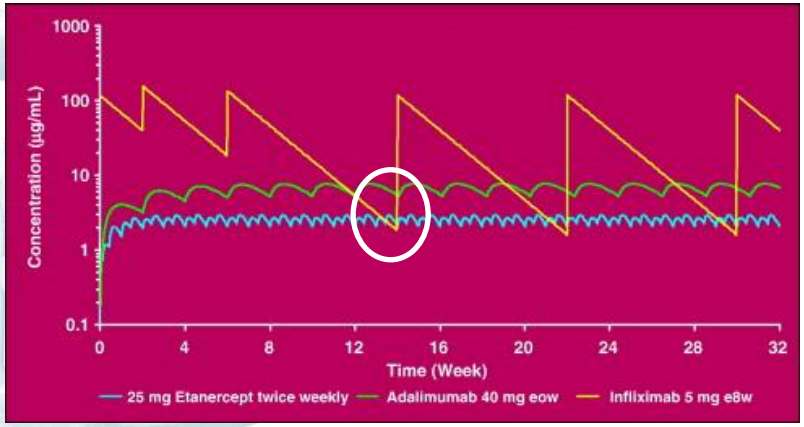
Humira®
adalimumab
(~95% human)

General introducion: infliximab

Infliximab

- Intravenous administration
- Dosage 5mg/kg every 8wks
- Trough levels (TL) = drug level in serum just before next iv

Pharmacokinetic profile of infliximab:



Adapted from Tracey D *et al.,* Pharm & Ther 2008

Response and loss of response

- 30% of patients are primary non-responders[1,2]
- 50% of patients lose clinical benefit over time (secondary non-responders)[1,2]
- Loss of response can be managed clinically by
  - Increasing dose
  - Decreasing intervals between iv
- Antibodies to infliximab (ATI) are seen in 5-18% of IBD patients under maintenance therapy[3]

1. Allez M *et al.*, JCC 2010; 2. Yanai H, Hanauer SB, AJG 2011; 3. Cassinotti A, Travis S, IBD 2009

How to measure TLI and ATI?

Trough level of IFX

- ELISA
- Cell based assay
- Radio Immuno Assay (RIA)
- Fluid phase mobility shift assay
- ...

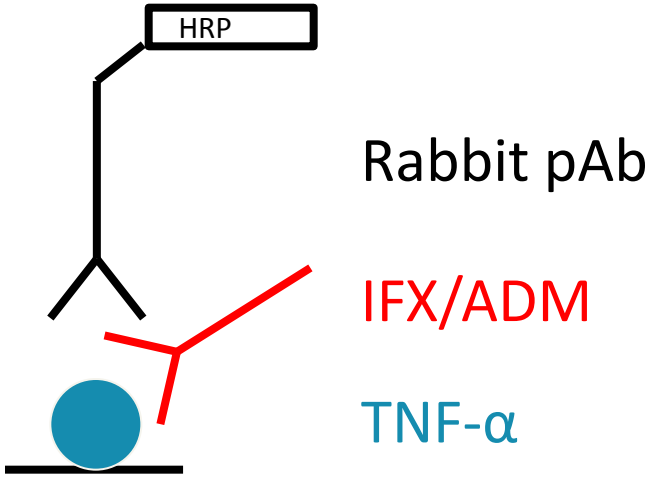
Antibodies to IFX

- ELISA
- Bridging ELISA
- Radio Immuno Assay (RIA)
- Surface Plasmon Resonance (SPR)
- Cell based assay
- Radio Immuno Assay (RIA)
- ...

In house developed and validated TL ELISA

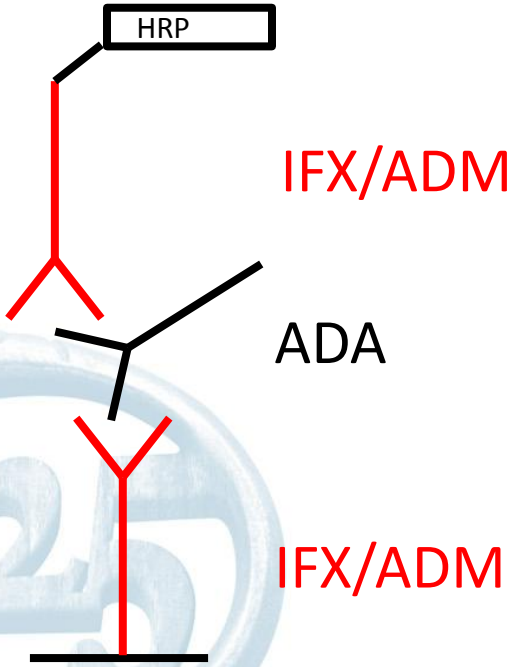
Trough level ELISA

- Advantages
  - Rapid
  - Cheap
  - Quantitative (expressed in µg/ml)
- Disadvantages
  - Does not detect drug in complex with anti drug antibodies (ADA)



In house developed ADA bridging ELISA

Anti Drug Antibody ELISA



- Advantages
  - Rapid
  - Cheap
  - Quantitative (expressed in µg/ml equivalents)
- Disadvantages
  - Drug interference
  - Unable to detect IgG4
  - Does not distinguish between neutralising and non-neutralising ADA

Validation of assays

Round robin experiment

-Samples from UMC Groningen, The Netherlands (Buurman DJ, Sturkenboom MGG, Kleibeuker JH, Dijkstra G) BMD kit

-Samples from Sanquin Amsterdam, The Netherlands (Rispens T, van der Kleij D) Sanquin assay

-Samples from University Hospitals Leuven, Belgium (Vande Casteele N, Vermeire S, Gils A) Leuven assay

Type of samples

Clinical samples (n=36)

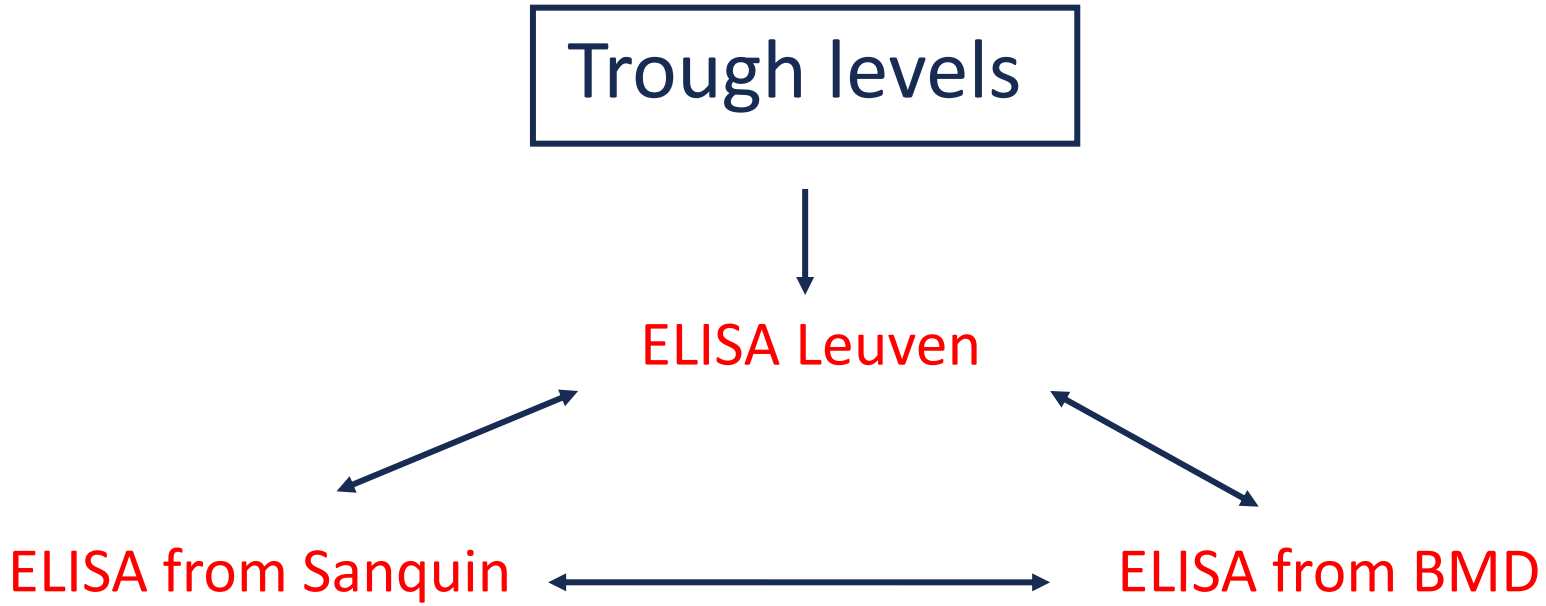
- Trough levels of IFX
  - Low
  - Intermediate
  - High
- Antibodies to IFX
  - Low
  - Intermediate
  - High

Quality control samples (n=26)

- Serum pool of healthy controls spiked with:
  - IFX
  - Antibodies to infliximab (ATI)
  - Antibodies to adalimumab (ATA)

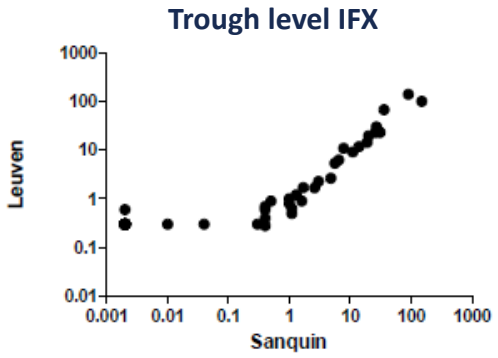
ALL SAMPLES WERE BLINDED

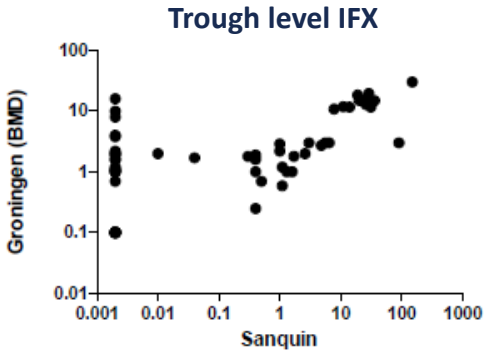
Validation of assays

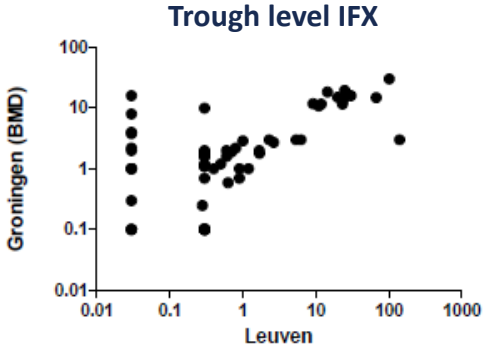


Validation of assays: trough level results

- Quantitative correlation:
  - Leuven *vs.* Sanquin: R^2=0,829 (P<0,001)
  - BMD *vs.* Sanquin: R^2=0,529 (P<0,001)
  - BMD *vs.* Leuven: R^2=0,349 (P<0,001)



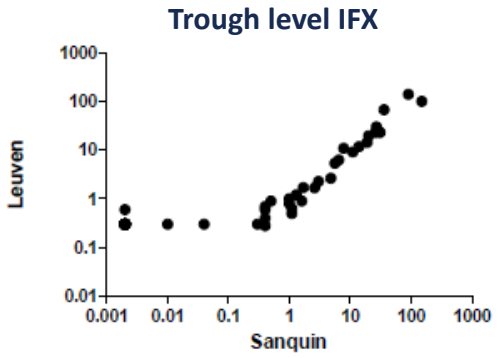


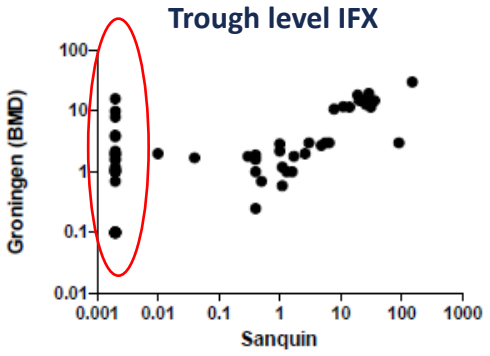


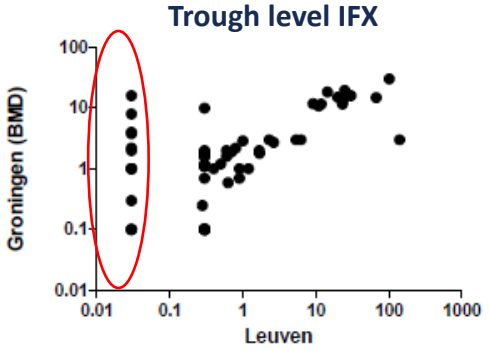
Unpublished data

Validation of assays: trough level results

- Quantitative correlation:
  - Leuven *vs.* Sanquin: R^2=0,829 (P<0,001)
  - BMD *vs.* Sanquin: R^2=0,529 (P<0,001)
  - BMD *vs.* Leuven: R^2=0,349 (P<0,001)
- Qualitative correlation:
  - BMD detected TLI in seven clinical samples in which the other two tests detected high ATI.
  - BMD detected TLI in six QC samples of which:
    - three were spiked with ATI
    - three were spiked with ATA

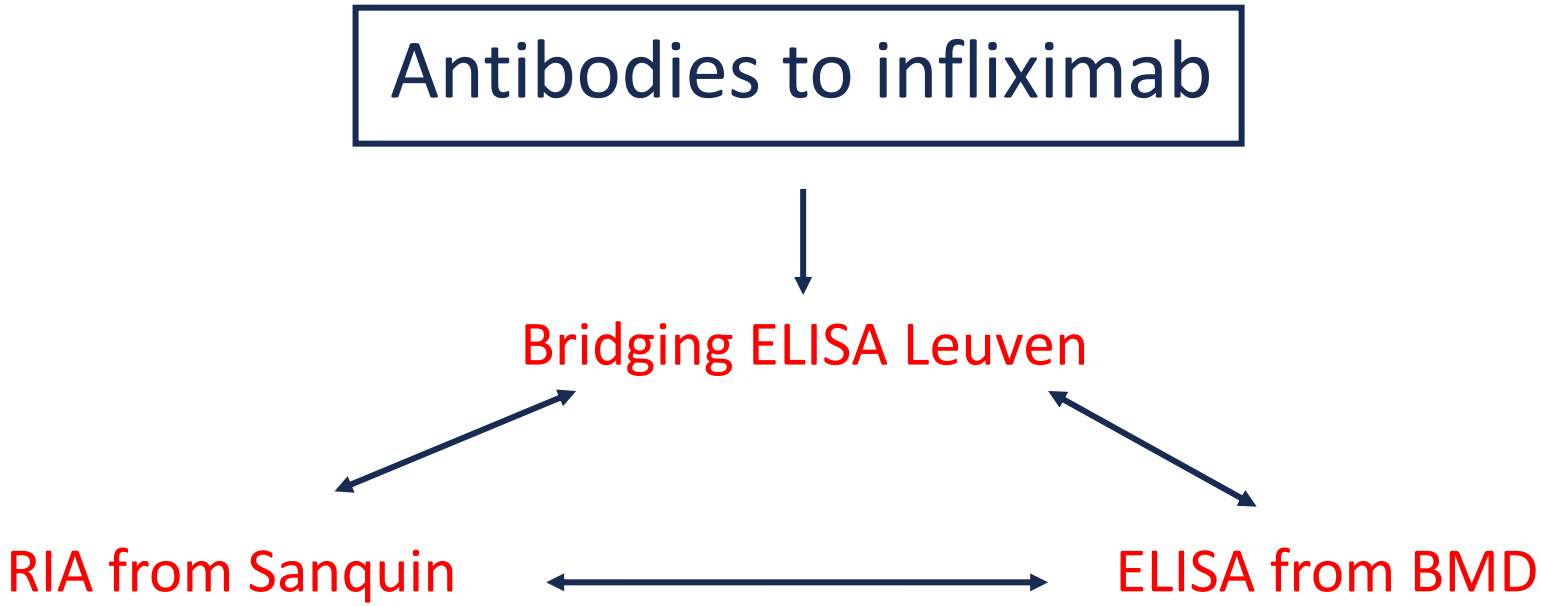






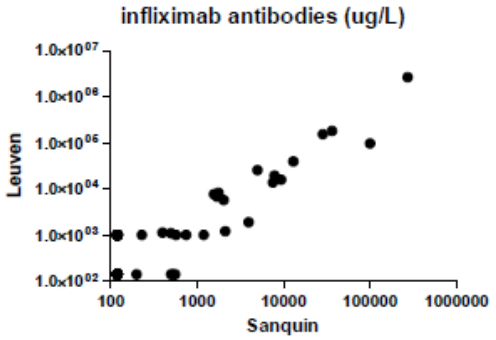
Unpublished data

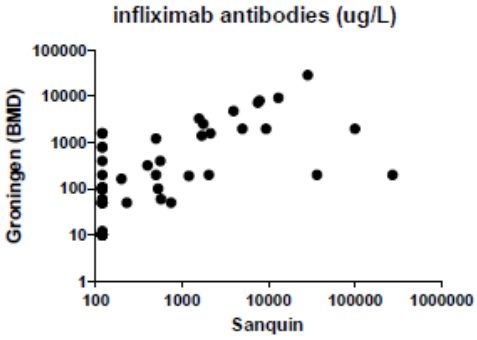
Validation of assays

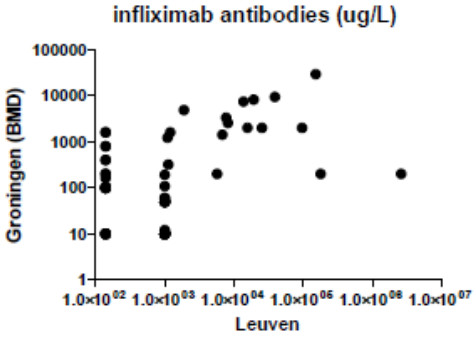


Validation of assays: anti drug antibody results

- Quantitative correlation:
  - Leuven *vs.* Sanquin: R^2=0,900 (P<0,001)
  - BMD *vs.* Sanquin: R^2=0,007 (P=0,541)
  - BMD *vs.* Leuven: R^2=0,002 (P=0,851)





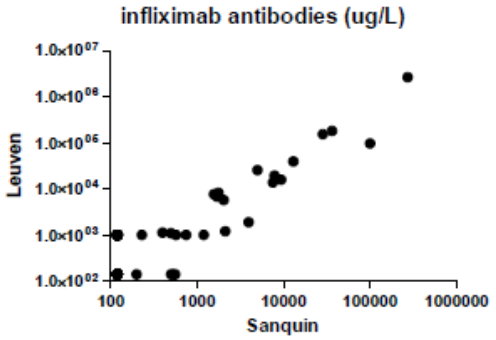


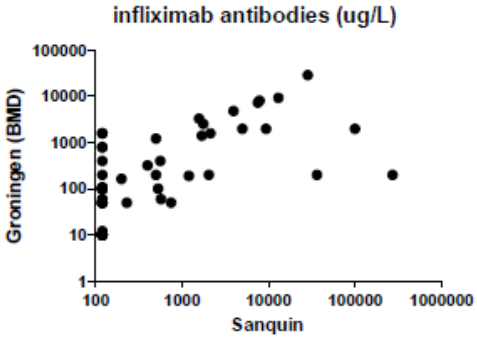
Unpublished data

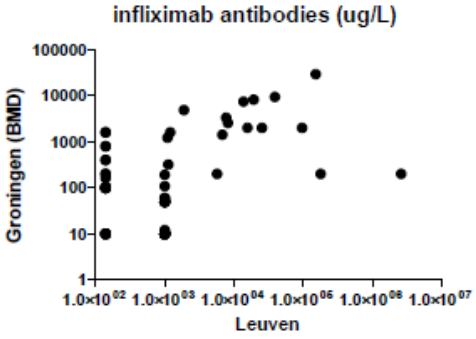
Validation of assays: anti drug antibody results

- Quantitative correlation:
  - Leuven *vs.* Sanquin: R^2=0,900 (P<0,001)
  - BMD *vs.* Sanquin: R^2=0,007 (P=0,541)
  - BMD *vs.* Leuven: R^2=0,002 (P=0,851)

- Qualitative correlation:
  - Leuven was not able to detect low level ATI in five samples that were detected by Sanquin and BMD.
  - RIA of Sanquin could detect lower ATI compared to ELISA from BMD and Leuven.







Unpublished data

Conclusion of the validation of assays

- ✓ There is a very good correlation of TLI and ATI measurements between assays developed by Sanquin and Leuven.
- ✓ The RIA appears to be superior to the ELISA from Leuven and BMD in detecting low ATI levels.
- ✓ TLI results of the BMD kit did correlate with Sanquin and Leuven, however the BMD kit showed false positive TLI results in quality control samples only containing ATI or ATA.

KATHOLIEKE UNIVERSITEIT
LEUVEN

Transient antibodies to infliximab: a retrospective case-control study in inflammatory bowel disease patients

Introduction and hypothesis

- Infliximab (Remicade), an IgG1 monoclonal chimeric antibody towards TNF-alpha can provoke an immunogenic response in IBD and RA patients.

- It has been shown that antibodies to infliximab can be transient (Aarden L. *et al.,* 2008).

- Factors influencing transiency/persistency are unknown.

- Hypothesis: in patients who develop only low titers of ATI, ATI can disappear and patients can recapture the effect of the drug.

Aims

- To provide more insight into antibody formation to infliximab by determining **TLI and ATI** in consecutive serum samples of IBD patients.

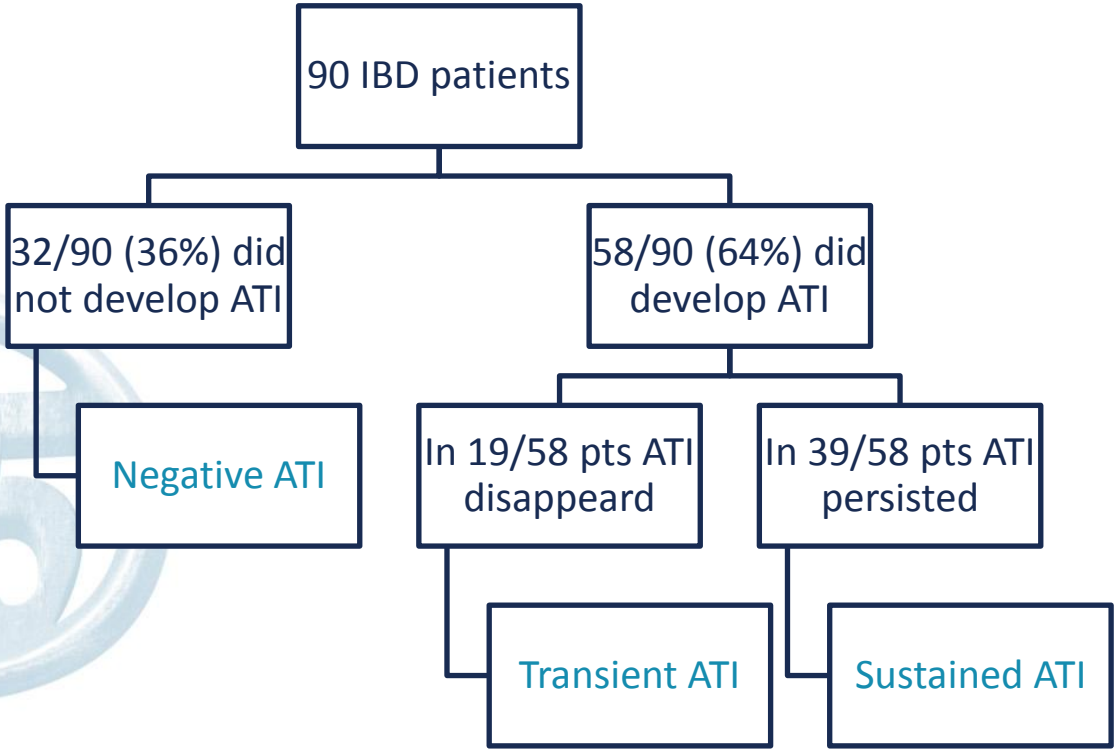
- To investigate **risk/protective factors** influencing antibody formation by linking them to clinical data and CRP.

- To formulate **guidelines** which can be used in clinical practice to help clinicians interpret ATI levels and to act accordingly.

Study design

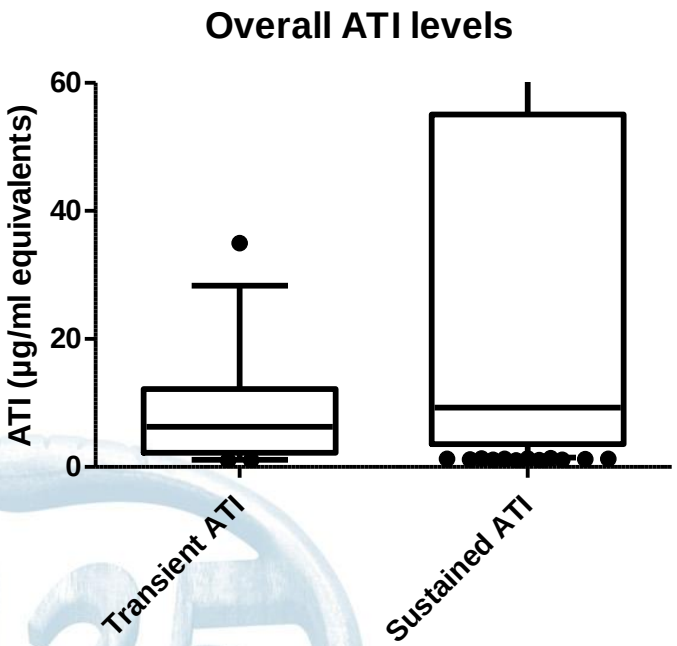
- Retrospective study of 90 IFX-treated IBD patients.

- All consecutive serum samples were analysed (1235 samples) for TLI and ATI with our in-house developed ELISA.



Unpublished data

Antibodies to infliximab



- ✓ Patients with sustained ATI had significantly higher ATI levels overall compared to patients with transient ATI:
  - ✓ 9.3 µg/ml; IQR 3.6-52.6

  vs.

  - ✓ 6.3 µg/ml; IQR 2.3-11.7

  P<0,001

Unpublished data

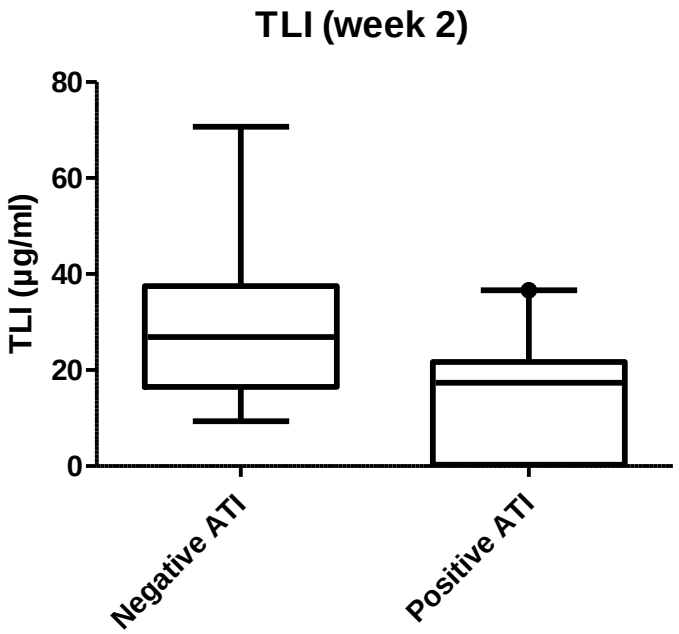
Trough levels of infliximab

- ✓ Patients who underwent an induction regimen (IV at week 0, 2, 6, 14) at start of IFX and did not develop ATI had significantly higher TLI at week 2:
  - ✓ 26.9 µg/ml; IQR 17.8-37.1

  vs.
  - ✓ 17.3 µg/ml; IQR 0.6-21.0

  P=0.01

- ✓ No difference between transient/sustained ATI



Unpublished data

Conclusions

- ✓ Low IFX trough levels at week two can be a **predictive factor** for the formation of antibodies to infliximab.
- ✓ **Low level ATI** can be **overcome** and patients can recapture response to infliximab.
- ✓ **High level ATI** lead however to a higher risk of adverse events and necessitate **treatment stop**.
- ✓ We advise to measure trough levels and antibodies to infliximab early on in the treatment and on a consecutive basis.

Unpublished data

KATHOLIEKE UNIVERSITEIT
LEUVEN

Personalised infliximab treatment using therapeutic drug monitoring: the prospective controlled Trough level Adapted infliXImab Treatment (TAXIT) trial

Introduction and hypothesis

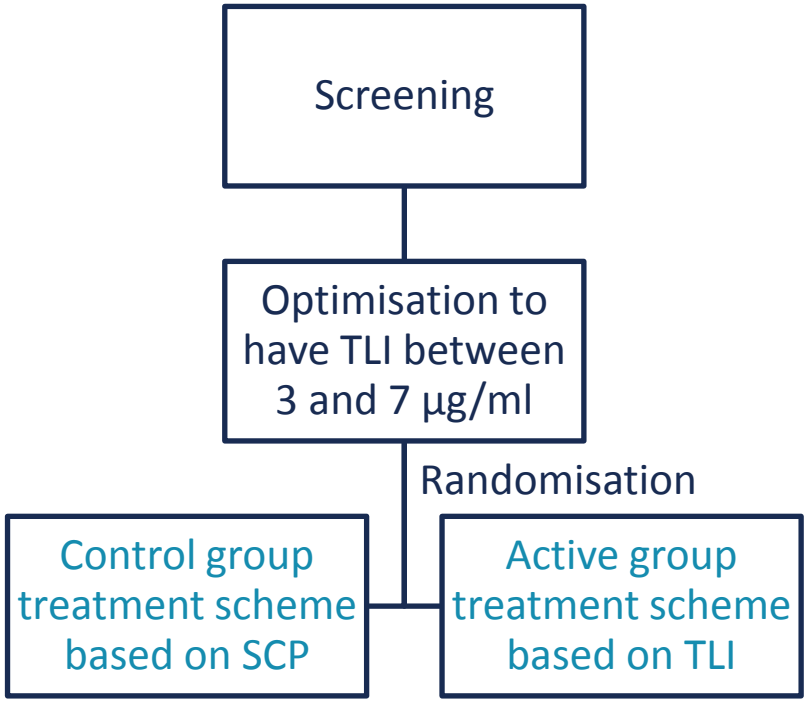
- Depending on patient's disease state, immunogenicity, metabolism, clearance; therapeutic drug levels can show great inter-individual differences.
  - Low trough levels -> disease flare, loss of response
  - High trough levels -> skin manifestations, arthralgias, high cost for healthcare payer

- **Objective parameter to assess efficacy of current treatment with anti-TNF biologicals in IBD is lacking.**

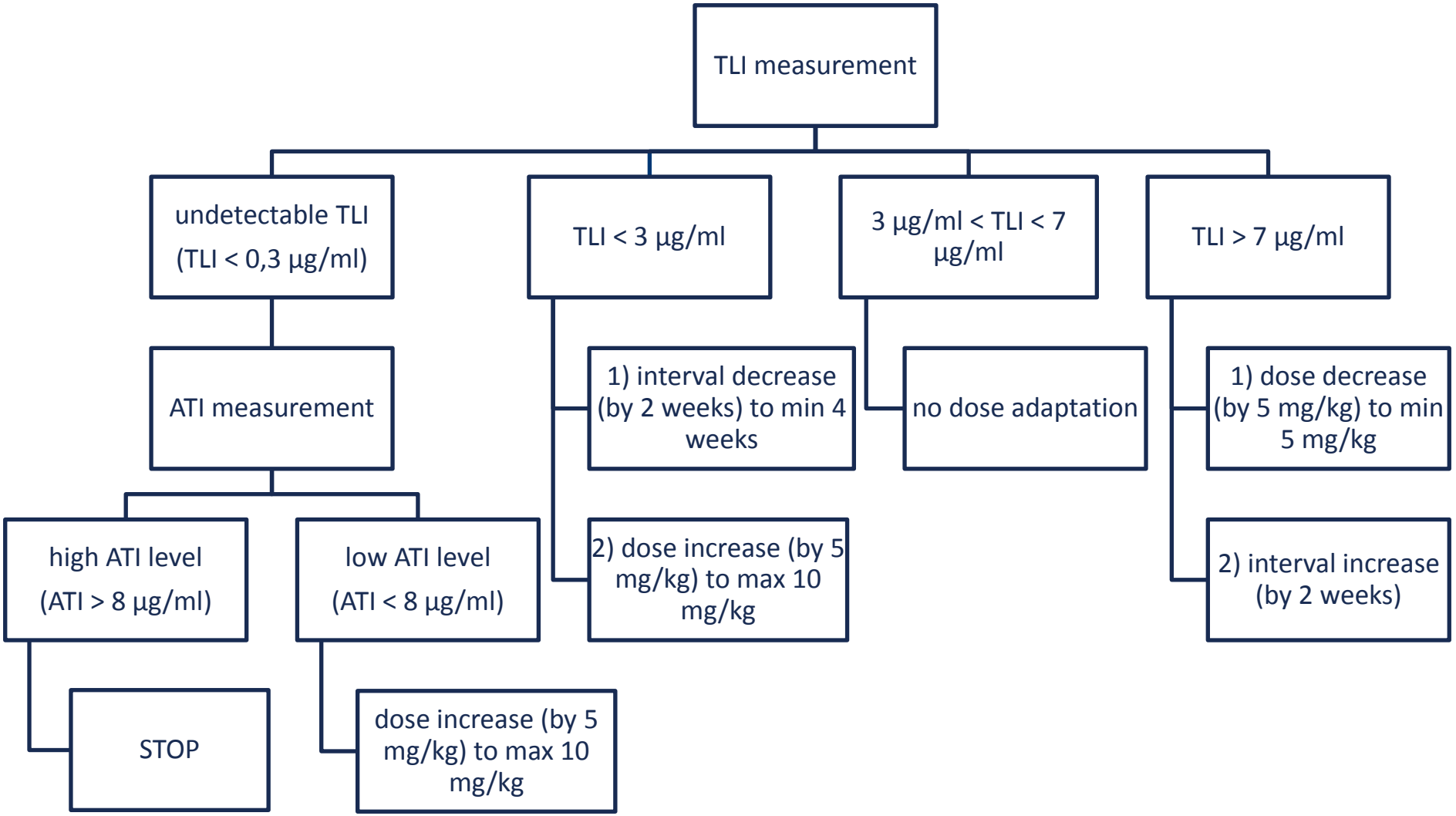
- We hypothesize that in patients suffering from Crohn's disease or ulcerative colitis under IFX maintenance therapy, sustained good IFX trough levels are associated with:
  - better response and remission rates
  - more mucosal healing
  - less loss of response

Study outline

- ✓ Self-funded monocentric prospective controlled trial
- ✓ Consecutive cohort of CD and UC responder patients on maintenance IFX
- ✓ Included between August 1st 2011 and October 27th 2011
- ✓ Clinicians and patients were blinded



TAXIT algorithm



TLI and ATI were measured with validated in-house developed sandwich and bridging ELISA

Study outline

- Primary endpoint was defined as clinical and biological (CRP < 5 mg/l) remission rates at one year after randomisation
- Secondary endpoints
  - **Mucosal healing assessed by endoscopy in both groups**
  - Proportion of patients with TLI within optimal interval
  - Proportion of patients needing to switch to adalimumab
  - The number of treatment adaptations in both groups
  - The number of adverse events in both groups
  - The number of infusion reactions in both groups
  - The number of disease flares in both groups
  - The median biologic activity (CRP-levels) in both groups
  - The total amount of IFX given in both groups
  - **Pharmacoeconomical cost of treatment in both groups**

SAFETY **TOLERABILITY** **EFFICACY**

Inclusion phase

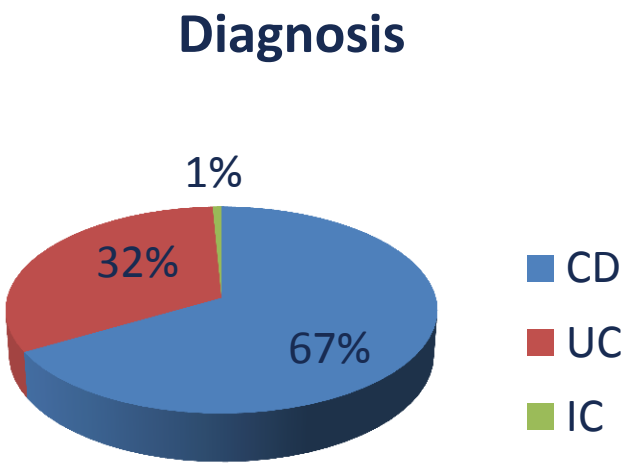
Inclusion criteria:

- ✓ 18 ≥ Age ≤ 64 years
- ✓ IBD diagnosis
- ✓ Stable clinical remission
- ✓ Informed consent
- ✓ On IFX for min. 14 weeks

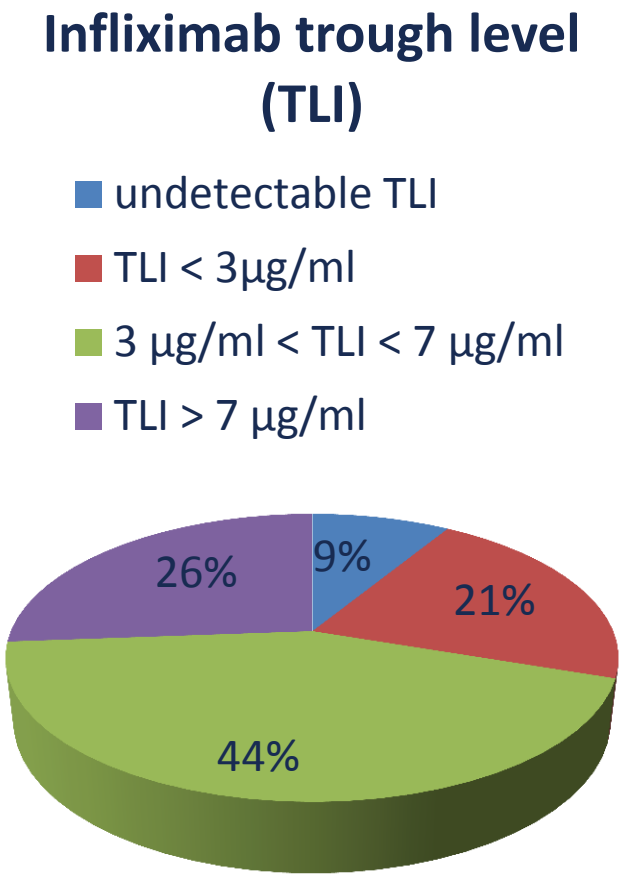
Exclusion criteria:

- ✓ Not meeting incl. criteria
- ✓ Enrolled in other CT

275 IBD patients in clinical remission and under IFX maintenance therapy were included:



Distribution of TLI at time of screening



Optimisation phase

275 pts screened

121/275 (44%) pts: TLI within interval

Randomised to control or active group

154/275 (56%) pts: TLI not within interval

18/154 (12%) pts could not be optimised

6/18 pts due to active disease

6/18 pts due to ATI > 8 µg/ml

6/18 pts due to not willing to adapt

21/154 (13%) pts still in optimisation

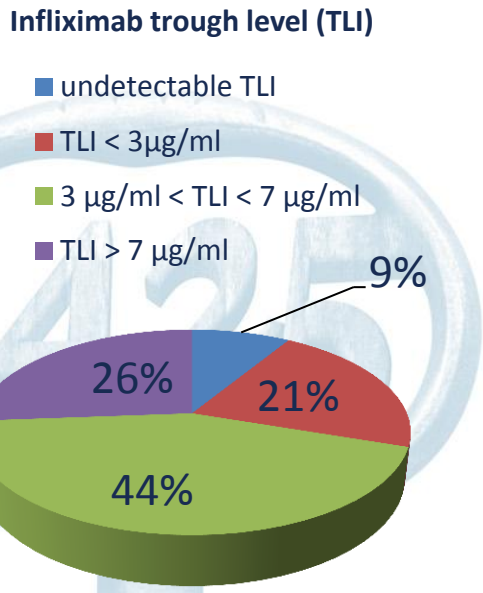
9/21 pts had ATI < 8µg/ml

6/21 pts could go to 12 week interval

6/21 intention to treat was not followed

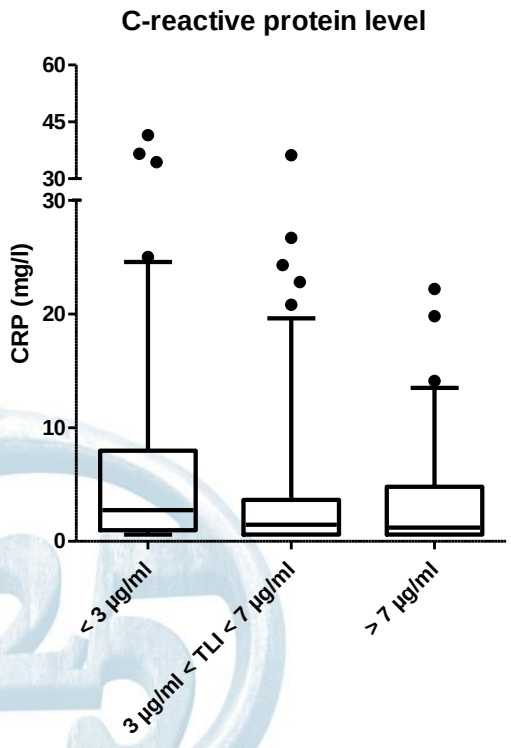
115/154 (75%) pts were optimised

Randomised to control or active group



Correlation between CRP and TLI at baseline

Measure for active disease



Comparing TLI *vs.* CRP

- ✓ Median (Q1-Q3) CRP levels in three groups:
  - ✓ TLI<3µg/ml: 2,7mg/l (IQR 1,1-7,5)
  - ✓ Optimal TLI: 1,5 mg/l (IQR 0,60-3,8)**
  - ✓ TLI>7µg/ml: 1,2 mg/l (0,6-4,8)*

Mann-Whitney U:
*p-value < 0,01 compared to TLI<3µg/ml
**p-value < 0,001 compared to TLI<3µg/ml

Conclusions

- ✓ In this large cohort of patients in remission under treatment with maintenance infliximab only 44% had optimal TLI and in all others dose adjustments were carried out.
- ✓ 9% of the patients had undetectable TLI despite staying in clinical remission.
- ✓ Due to screening for TLI and ATI, we could stop IFX treatment in 6 patients in whom ATI > 8 µg/ml (some patients already had **ATI for more than 2 years**).
- ✓ The current controlled study will show whether long term adjustment of treatment based on IFX levels is a superior strategy.

Acknowledgements

- The laboratory for Pharmaceutical Biology
  - ✓ Griet Compernolle
  - ✓ Nick Geukens, PhD
  - ✓ Miet Peeters
  - ✓ Marlies Van de Wouwer, PhD
  - ✓ Niels Vande Casteele
  - ✓ Paul Declerck, PhD
  - ✓ **Ann Gils, PhD** (ann.gils@pharm.kuleuven.be)
- The Leuven IBD research group
  - ✓ Filip Baert, MD
  - ✓ Vera Ballet
  - ✓ Isabelle Cleynen, PhD
  - ✓ Tamara Coopmans
  - ✓ Marc Ferrante, MD, PhD
  - ✓ **Paul Rutgeerts, MD, PhD**
  - ✓ **Gert Van Assche, MD, PhD**
  - ✓ **Severine Vermeire, MD, PhD**
- Infusion unit University Hospitals Leuven
  - ✓ Ingrid De Wolf
  - ✓ Hilde Vanderschelde
  - ✓ Marie-Josee Vermeyen
  - ✓ Anita Vleminckx
  - ✓ Ellen Weyts
- University Medical Center of Groningen
  - ✓ Dorien Buuran, MD
  - ✓ Gerard Dijkstra, MD PhD
  - ✓ J.H. Kleibeuker, MD, PhD
  - ✓ Marieke Sturkenboom
- Sanquin Amsterdam, diagnostics laboratory for Allergy and Monoclonal Therapeutics
  - ✓ Theo Rispens, PhD
  - ✓ D. van der Kleij, PhD

KATHOLIEKE UNIVERSITEIT
LEUVEN

Niels Vande Casteele

Katholieke Universiteit Leuven
Department of Pharmaceutical and Pharmacological Sciences

Laboratory for Pharmaceutical Biology
Herestraat 49 box 824
3000 Leuven – Belgium
T +32 16 32 34 34
F +32 16 32 34 60
E niels.vandecasteele@pharm.kuleuven.be

http://pharmabs.org
www.ibd-kuleuven.com