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INNOVATIONacademy

Monitoring Anti-TNFα drugs in chronic inflammatory diseases - impact on tailoring therapies

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Outline

- What are biologics?
- What are they licensed for in the UK?
- Cost to healthcare and disease burden
- Why are we interested in measuring these drugs and antibodies against them?
- Service review
- Clinical utility and case studies
- Conclusions

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Biologicals

- Native proteins like
  - hormones
  - cytokines
  - growth factors or
- Engineered molecules
  - Therapeutic antibodies
  - Antibody fragments
  - Protein constructs
- More than 30 Ab and Ab derivatives have been approved
- Several clinical trials in various therapeutic indications, particularly oncology and autoimmune disease

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TNF alpha

- Proinflammatory cytokine
- Plays a key role in the inflammatory processes involved in autoimmune diseases
- Inflammatory Bowel Disease (IBD) – characterised by dysregulated mucosal immuno-response in genetically susceptible individuals
- Immune dysregulation results in overproduction of TNF alpha by monocytes, macrophages and T cells
- Monoclonal antibodies (infliximab, adalimumab and certolizumab) targeting TNF alpha induce the formation of regulatory macrophages with immunosupressive properties

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Biologics

Generic name	Trade name	Structure	Clinical Use
Infliximab	Remicade	Chimeric IgG1 kappa (30% mouse variable regions, 70% human constant regions)	CD, UC RA, PsA, AS Ps
Adalimumab	Humira	Humanised IgG1 kappa	CD, UC RA, JIA, PsA, AS Ps
Etanercept	Enbrel	Fusion protein of extracellular domain of TNF receptor 2 and human IgG1 F_c domain.	Ra, JIA, PsA, AS Ps
Certolizumab	Cimzia	PEGylated humanised F_{ab}' fragments	RA
Golimumab	Simponi	Recombinant human IgG1 kappa	RA, PsA, AS

CD = Crohn's disease, UC = Ulcerative Colitis, RA = Rheumatoid Arthritis, PsA = Psoriatic Arthritis, AS = Ankylosing Spondylitis, JIA = Juvenile Idiopathic Arthritis, Ps = Plaque Psoriasis.

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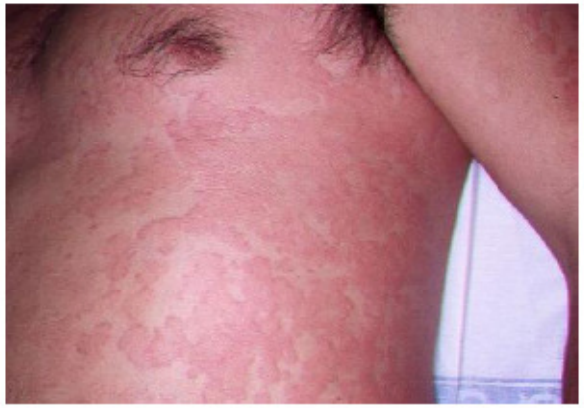
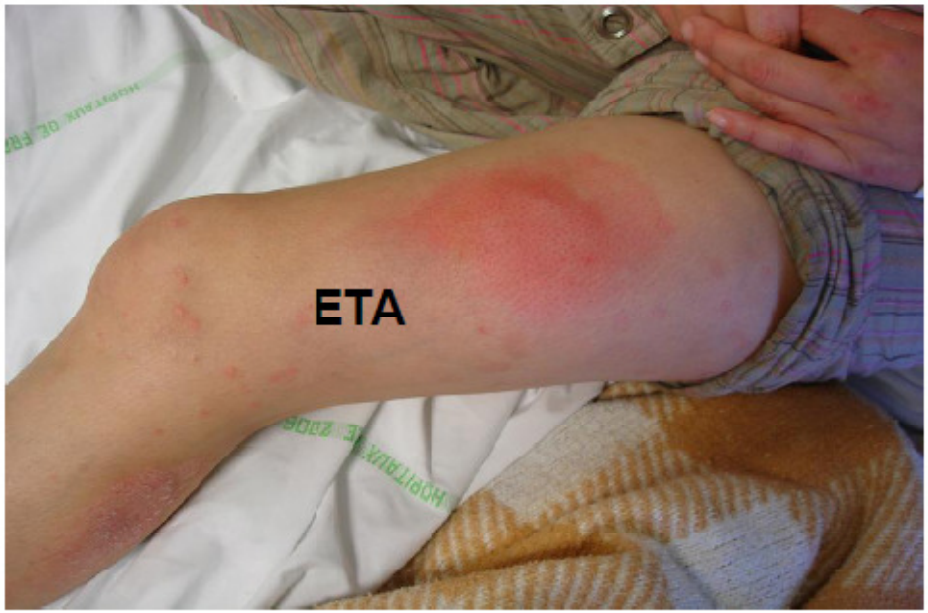
Route of administration and targets

- IV infusion
  - Remicade (Infliximab)
- Subcutaneous injection
  - Adalimumab (Humira
  - Etanercept (Enbrel)
  - Golimumab (Simponi
  - Ustekinumab (Stelera

Acute infusion reaction





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Factors affecting pharmacokinetics

Table 3 Factors affecting the pharmacokinetics of monoclonal antibodies

	Impact on pharmacokinetics
Presence of ADAs **(Anti-drug antibodies)**	Decreases serum (mAbs) Threefold-increased clearance Worse clinical outcomes
Concomitant use of IS **(Immunosupressants)**	Reduces ADA formation Increases serum (mAbs) Decreases mAbs clearance Better clinical outcomes
High baseline (TNF-α)	May decrease (mAbs) by increasing clearance
Low albumin	Increases clearance Worse clinical outcomes
High baseline CRP	Increases clearance
Body size	High body mass index may increase clearance
Gender	Males have higher clearance

ADA, antidrug antibody; CRP, C-reactive protein; IS, immunosuppressive agent; mAb, monoclonal antibody; TNF-α, tumor necrosis factor-α. Terms in parentheses refer to serum concentration.

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Crohn's Disease

- Chronic inflammatory disorder that is neither medically nor surgically "curable"
- Cause is multifactorial (combination of genetic predisposition and environmental factors)
- Can affect any age group but most commonly present in teens and twenties, median age at diagnosis is 29.5
- Goal of therapy
  - Elimination of all disease-related symptoms
  - Normalize the patients' quality of life
  - Maintain the general "well-being" of patients with as few side effects and long-term sequelae as possible
- Biologics and immune-modulating agents
  - Trough IFX levels associated with remission, CRP and mucosal healing

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Rheumatology – Rheumatoid Arthiritis (RA)

- Chronic ,systemic inflammatory disease affecting joints of the body, cause unknown
- Impacts heavily on people of working age (most common after 40)
- Major cause of sickness absence, and worklessness
- 1/3 rd of people with RA stop working within 2 years of diagnosis*
- Overall cost to UK economy (due to productivity losses) £8 billion per year

* National Audit Office (2009) Services for people with rheumatoid arthritis. London: The Stationery Office

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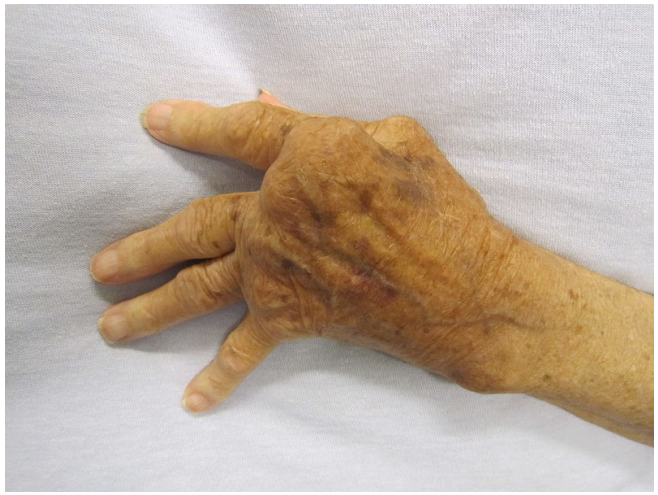
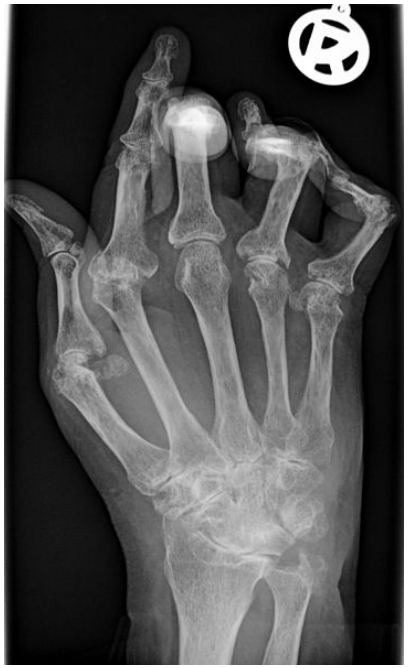
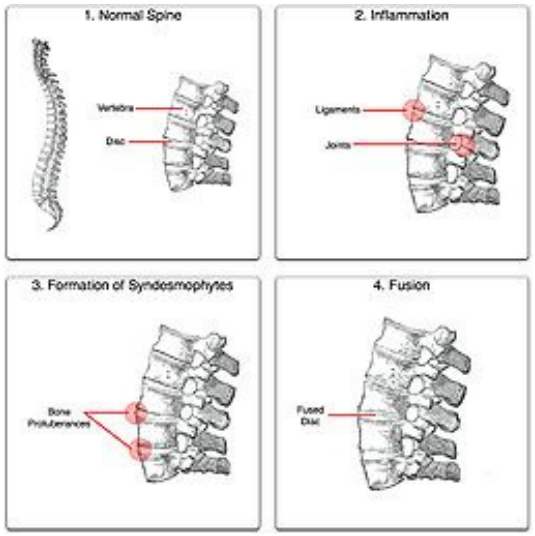
Rheumatology



Rheumatoid Arthritis



Psoriatic Arthritis



Ankylosing Spondylitis

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Inflammatory skin disease

- **Psoriasis;** chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations
- Plaque psoriasis is the commonest type of psoriasis representing 90% of the cases
- Up to 30% of patients with psoriasis also develop psoriatic arthiritis which causes pain, stiffness and swelling in and around the joints
- Major impact on quality of life

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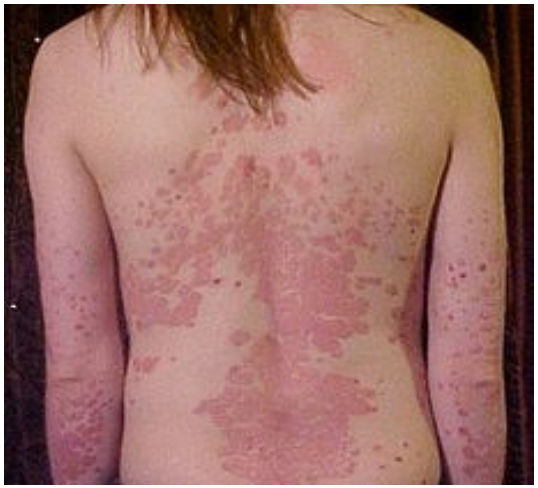
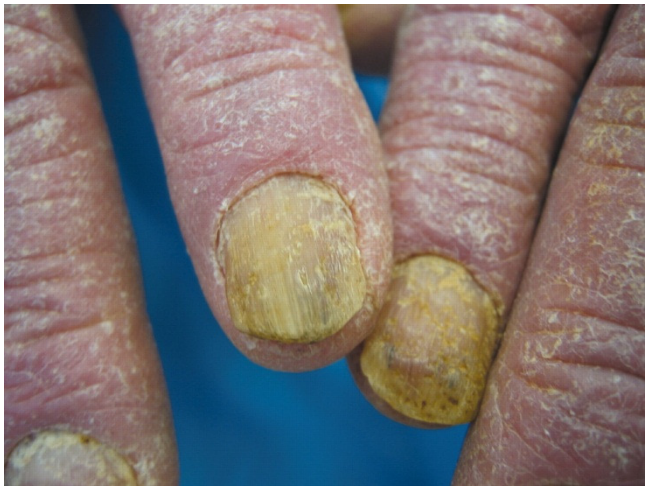
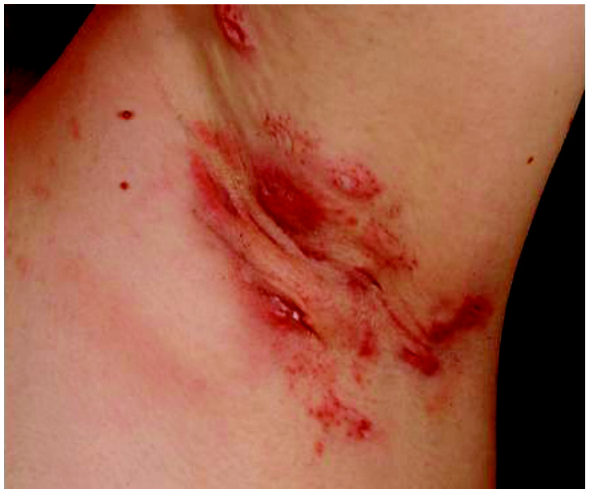
Dermatology



Plaque psoriasis.



Nail plates in a patient with psoriasis*



Hidradenitis Suppurativa

(off-licence)

*Langley R G B et al. Ann Rheum Dis 2005;64:ii18-ii23

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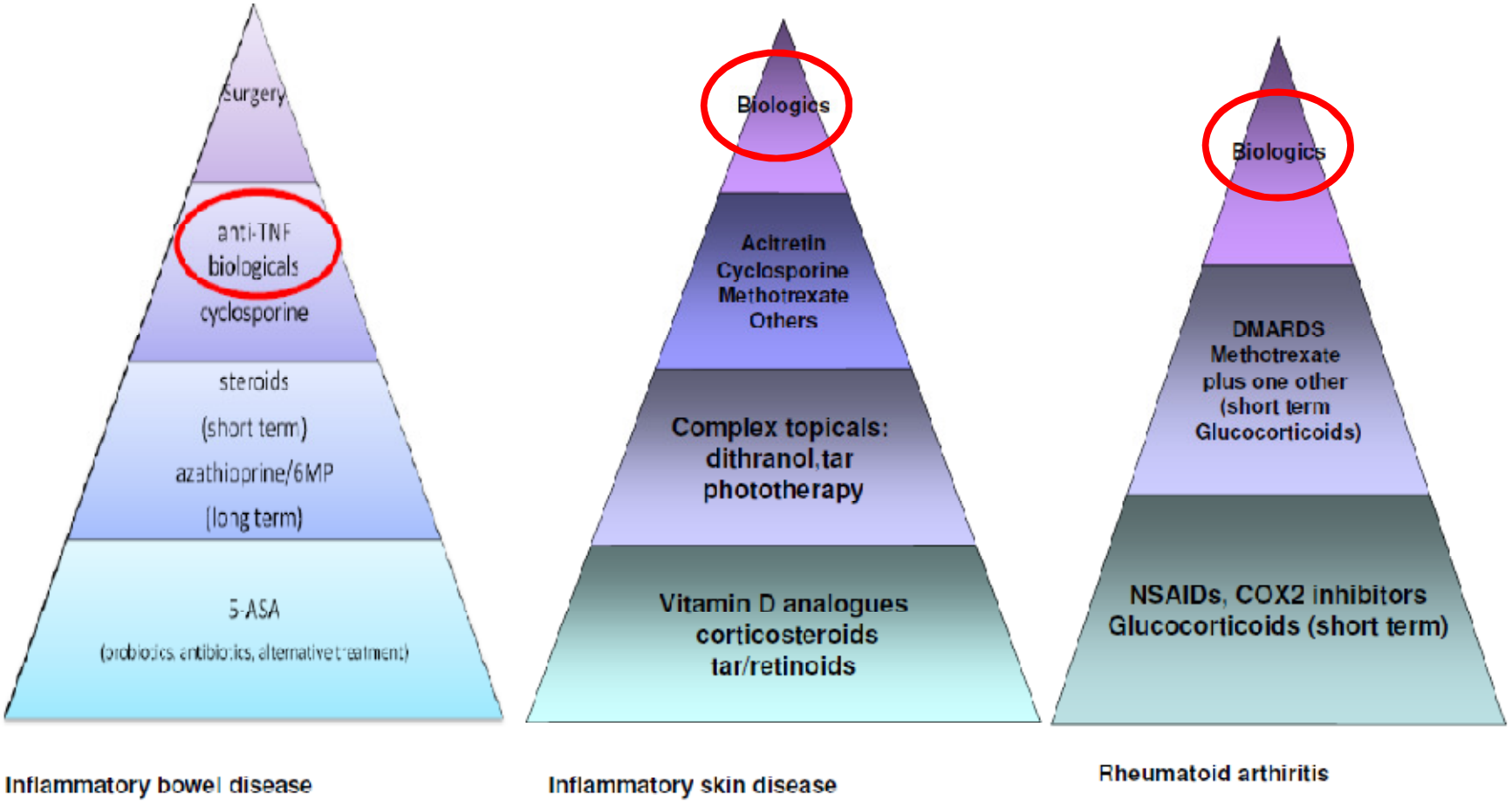
Treatment options as overview

NICE guidance – defines eligibility and stopping criteria for biologics

Average biologic therapy cost per patient/yr £10 -15K



Assumptions used in estimating population benchmark for biologics use in inflammatory diseases

Total number ~ 1.5 million people

Condition	Estimated number of people with the condition	Estimated number of people with the condition eligible and receiving treatment with biologic drugs	Estimated percentage of people with the condition eligible and receiving treatment with biologic drugs
Rheumatoid arthritis	350,000	35,000	10.0%
Ankylosing spondylitis	71,000	6,900	9.7%
Psoriatic arthritis	263,000	6,300	2.4%
Psoriasis	607,000	18,000	3.0%
Crohn's disease (adults)	81,000	10,500	13.0%
Ulcerative colitis	77,000	750	1.0%
Juvenile idiopathic arthritis	8,500	1,300	15.0%
Crohn's disease (children)	1,800	240	13.0%

Total number eligible for biologics ~ 80,000 people

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Loss of response

- Primary loss of response
  - Lack of improvement of clinical signs and symptoms during induction therapy (1/3 suffer primary response failure*)
- Secondary loss of response
  - Initial clinical response but eventually loss of response to therapy
  - Mechanisms are not fully clear in all cases
  - Inter-individual variation (drug bioavailability and pharmacokinetics)
  - Accelerated drug clearance in periods of high disease activity
  - Immunogenicity (loss of efficacy and safety)
- Therapeutic approaches
  - Use maintenance therapy rather than episodic administration
  - Concomitant therapy with immunosupressants (methotrexate, mercaptopurine and azathioprine)

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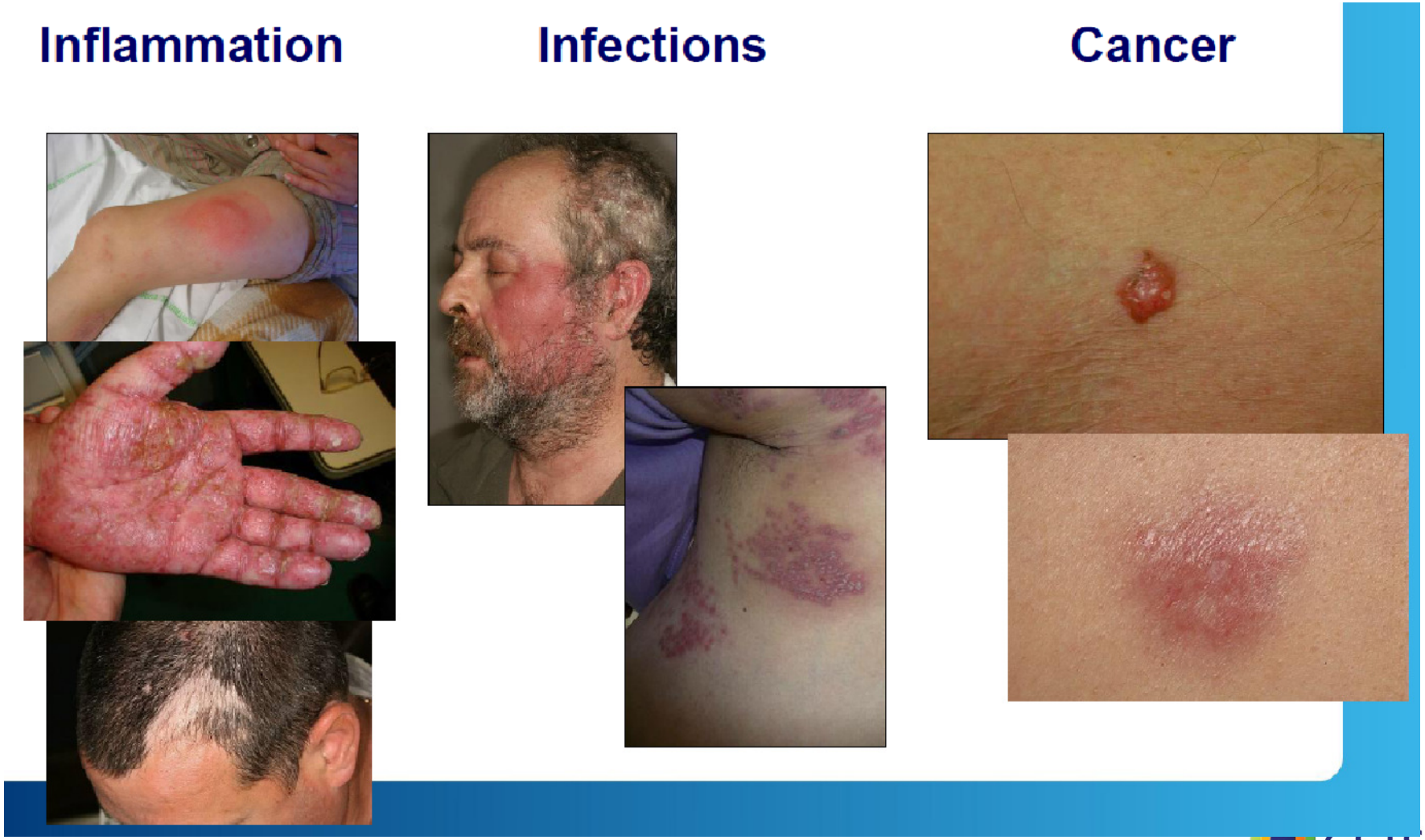
*** Allez *et al* J Crohns Colitis, 355 -366 (2010), Furst *et al,* Ann. Rheumatol. Dis. 70 (Suppl 1), I2-I36 (2011)**

Cutaneous side effects of anti-TNF therapy

Inflammation **Infections** **Cancer**



François Aubin European Crohn's and Colitis Organisation, Barcelona 2012

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Potential clinical applications of drug and ADAb measurement

- **Understanding the underlying cause of treatment failure**
- **Correlation of clinical findings with individual pharmacokinetics**
- **Aid in decision making:**

  - Primary or secondary loss of response, switching to alternative drug
  - Dose escalation/de-escalation
  - Drug reintroduction after drug interruption
  - Adherence to therapy
  - Confirmation of infusion or injection site reactions

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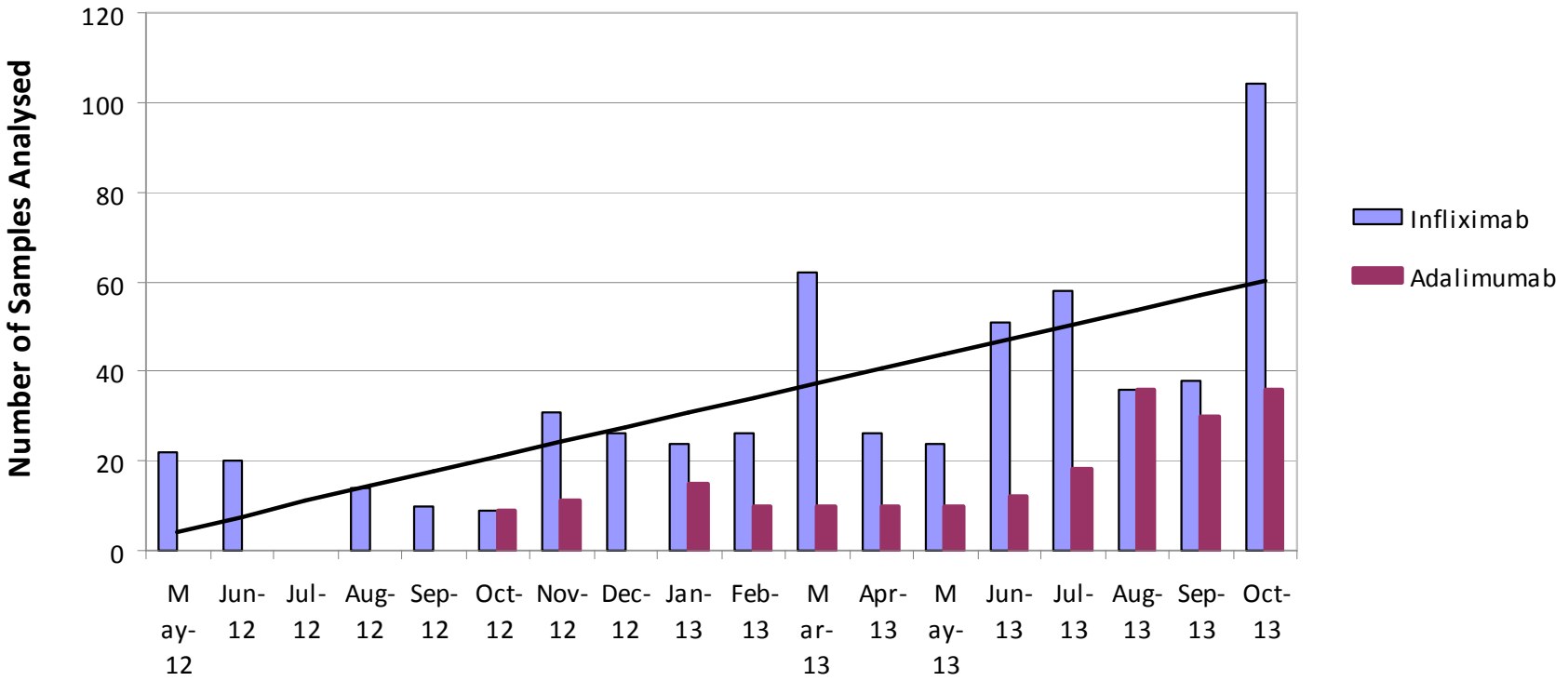
Service growth excluding research samples

Significant work had been done pre-implementation in collaboration with clinical colleagues



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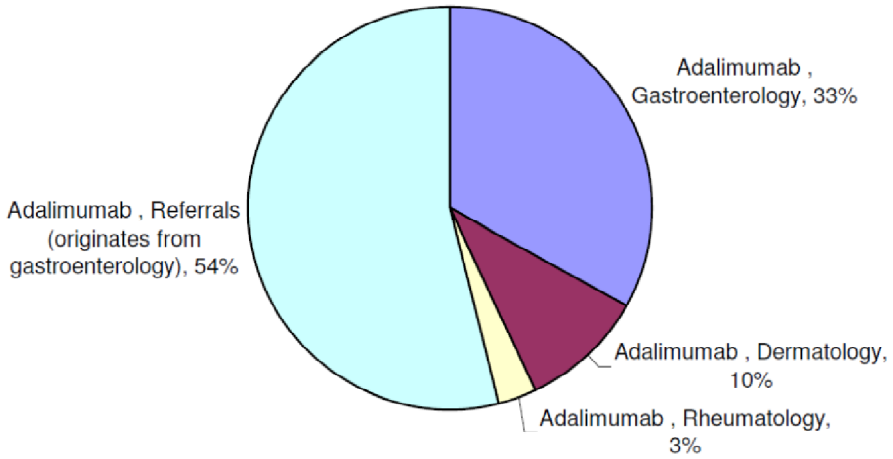
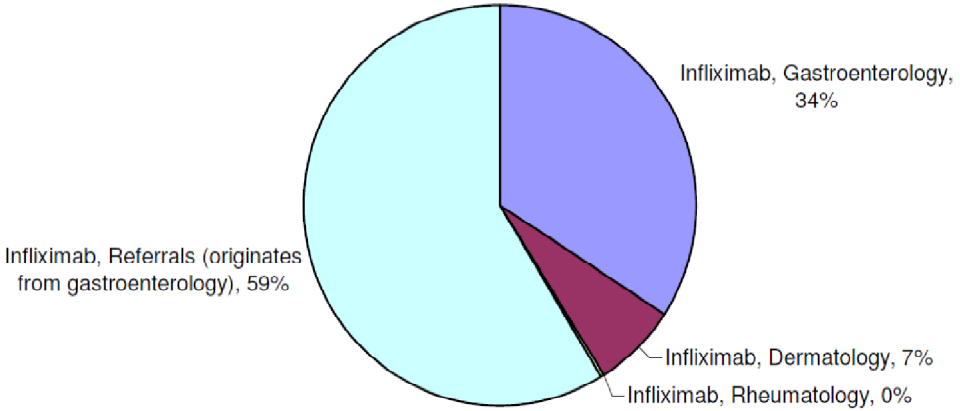
Source of requests : May 2012 to October 2013

Total no analysed for Adalimumab ~230



Total no analysed for Infliximab ~597



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Case 1: 32 yr Male diagnosed with Ulcerative colitis in 2001

- Intolerant of azathioprine and mercaptopurine at low doses, 4 courses of steroids since diagnosis
- Steroid dependent disease, also tried 6 months Methotrexate
- 6 infusion of Infliximab (5mg/kg), initial response and subsequent loss of response
- Infliximab = 0.8 µg/mL and anti-IFX-Ab >200 ng/mL

Decision making:

- Infliximab discontinued
- Discussion with patient: starting Tacrolimus or the more conventional therapy of surgery
- Put on Clipper (beclometasone dipropionate) and doing well
- Potential for Adalimumab trial

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Case 2: 30 yr Male Ileocolonic & perianal Crohn's Disease diagnosed in 2007

- 6 doses of infliximab in 2009, with good response
- Recurrent fistulising disease in June 2012
- Infliximab 5mg/kg Q8 commenced October 2012
- Azathioprine 50mg/25mg alternate days
- Nov 2012 – IFX <0.1 ug/mL, Anti-IFX-Ab >200 ng/mL
- Following second induction dose, patient developed a severe arthropathy and had active perianal disease

Decision making:

- Switch to Adalimumab 40mg every other week (Jan 2013)
- October 2013 , he remains well HBI= 0

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Case 3: 36 year old male with severe Hydradinitis Suppurativa

- Failed to respond to previous surgical and medical interventions
- Started on Infliximab 5 mg/kg 8-weekly (Q8)
- Patient responded well initially but eventually started developing symptoms prior to subsequent infusions
- Trough Infliximab levels were measured and found to be intermediate (1 – 2 µg/mL) with no ADAb

Decision making:

- Dose frequency was switched to 5 mg/kg 6-weekly (Q6)
- Clinically, patient improved to such a degree that he was able to return to work

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Conclusions

- **Biologic drugs have revolutionised the management of patients with severe, refractory inflammatory disease.**
- **Commercial assays are now available for the measurement of these drugs and their associated ADAb, however standardisation is lacking.**
- **Results generated through this service are enabling clinicians to take a more personalised approach to optimising the use of these expensive drugs and ensuring patient safety.**
- **Significant work to be done to provide access to drug and ADAb monitoring**
- **Complex area where clinical collaborative work is essential for offering an evidence-based laboratory service**

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Acknowledgements

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