Falta ou perda de resposta aos ant-TNFs. Qual o próximo passo

Silvio Danese

Anti-TNF α for IBD: current knowledge

	Infliximab	Adalimumab
Type	chimeric	human
Administration	i.v.	s.c.
Frequency	Q8	Q2
Efficacy in luminal CD	yes	yes
Efficacy in CS sparing	yes	yes
Fistula healing	yes	yes (not licensed)
Efficacy in UC	yes	yes
MH	yes	yes
Paediatric CD	yes	yes
Paediatric UC	yes	being studied
Benefit/risk	favorable	favorable

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$\approx < 1/3$
at 1 yr

Optimization of anti-TNF treatment

- Once anti-TNF has started, how to avoid and manage primary failure?

❖ Problem: how should we define primary failure?

- Broad range of "response intensity" (no clinical response, no clinical remission, no steroid-free clinical remission, no MH....)

Allez M, et al. JCC 2010; D'Haens G, et al. AJG 2011

Primary non-response to anti-TNF alpha

PREDICTORS

- Longer (>2 years) disease - duration or small bowel disease
- Smoking- (not in fistulizing disease)-
- Complicated phenotype-
- ANCA/ASCA status (UC)-
- Normal CRP —
- Low Hb (<9.4)- (single UC study)-
- Genetic- (IBD5 mutation, FAS-L and - Caspase 9 mutations, Non FC-gammaRIIIa genotype)

Ben Horin S, et al. Autoimm Rev 2014

20-40% of IBD patients in clinical trials
10-20% of IBD patients in clinical 'real life' series

Hanauer SB, et al. Lancet 2002; Rutgeerts P, et al. NEJM 2005; Hanauer SB, et al. Gastroenterology 2006; Colombel JF, et al. Gastroenterology 2007; Rudolph SJ, Dig Dis Sci 2008; Afif W, et al. IBD 2009; Schnitzler F, et al. Gut 2009; Cussalah A, et al. AJG 2010; Kiss LS, et al. APT 2011; Reinisch W, et al. Gut 2011; Ben Horin S, et al. Autoimm Rev 2014

Primary failures with anti-TNF alpha

Conclusion

Definition

Prevention

- Patient selection
- Optimal induction regimen
- Consider IS and/or steroid co-treatment?

Prediction?

Management:

- Identification
- Consider all therapeutic options, including surgery
- Switch in-class
- Switch out-of-class (clinical trials; VDZ, UST)
- Other options in very difficult situations

Optimization of anti-TNF treatment

- Once anti-TNF has been successfully started, how to avoid or manage secondary failure and/or suboptimal treatment?

❖ Definition (two key features):

- 1) Re-emerging symptoms appear in a patient whose disease was controlled by induction treatment
- 2) These symptoms are due to inflammatory process attributable to the underlying IBD

Allez M, et al. JCC 2010; Ben Horin S, et al. APT 2011

Mechanisms of worsening on anti-TNFs

Non-inflammatory mechanisms

- IBS
- Fibrostenotic strictures
- Cancer
- Dietary (e.g. lactose)
- Miscellaneous (e.g. amyloidosis, SIBO, Bile salt diarrhoea)

Inflammatory mechanisms

Non-IBD related inflammation

- Infection
- Ischemic colitis
- Vasculitis

Un-controlled IBD inflammation (inadequate anti-TNF in serum)

- Loss of anti-TNF activity due to ADA
- Relentless TNF-mediated flare «consuming» the anti-TNF drug
- Loss of anti-TNF activity due to non-immune drug clearance
- Non-adherence to anti-TNF treatment

Un-controlled IBD inflammation (adequate anti-TNF in serum)

- Paradoxical exacerbation of inflammation by anti-TNFs
- Shift of disease pathway away from TNF to other mediators

Adapted from Allez M, et al. JCC 2010; Ben Horin S, et al. Autoimm Rev 2014

Loss of response to anti-TNF alpha

Infliximab
13% per patient-year of FU
(annual risk)

Adalimumab
20% per patient-year of FU
(annual risk)

12-month Loss of response in
case series and in RCTs
ranges between 23% and 46%

Ben-Horin S, et al. APT 2011

Gisbert JP, et al. AJG 2009; Billioud V, et al. AJG 2011

Optimization of anti-TNF treatment to prevent loss of response

- Chimeric / Humanized / Fully human biologics (No)
- Adequate induction doses and scheduled maintenance Tx (Yes)
- Concomitant Immunomodulators (¿Yes?)
 - For IFX: better outcome for combo in IM naïve patients (SONIC, SUCCESS, Steroid-dependent UC)
 - No RCT data with ADA
 - No RCT in patients failing IMM drugs
 - Conflicting results in retrospective cohorts (++/- -)
 - No consensus on duration of combo therapy: for ever or 6 month?
 - Consider adverse events

Vermeire S, et al. Gut 2007; Regueiro M, et al. IBD 2008; Hanauer SB, et al. CGH 2006; Baert F, et al. NEJM 2003; Farrel RJ, et al. Gastroenterology 2003; Schnitzler F, et al. Gut 2009; Sokol H, et al. Gut 2010; Reenaers C, et al. APT 2012; Colombel JF, et al. NEJM 2010; Panaccione R, et al. ECCO 2011; Armuzzi A, et al. IBD 2013; Kestens C, et al. CGH 2013; van der Valk ME, et al. Gut 2012; Baert F, et al. JCC 2013; Kiss LS, et al. APT 2011; Abraham NS, et al. CGH 2013;

Factors affecting the PK of mAbs

Impact on PK	
Presence of ADAs	Decrease serum mAbs Threefold increase clearance Worse clinical outcome
Concomitant IS	Reduces ADA formation Increases serum mAbs Decreases mAbs clearance Better clinical outcome
High baseline TNF	Increase mAbs clearance
Low albumin	Increase mAbs clearance Worse clinical outcome
High baseline CRP	Increase mAbs clearance
Body size	High BMI increases clearance
Gender	Males have higher clearance

Orda

Managing loss of response – Dose intensification

Ben-Horin S, et al. APT 2011

Katz L, et al. IBD 2012

Anti-adhesion therapies for IBD

Lobaton T, et al. Aliment Pharmacol Ther 2014;39:579-94

Vedolizumab is a novel gut-selective anti-inflammatory biologic

- Humanized mAb that binds exclusively to the $\alpha 4\beta 7$ integrin heterodimer
 - Does not bind to $\alpha 4\beta 1$ or $\alpha E\beta 7$ integrin¹
- Selective antagonist of $\alpha 4\beta 7$ integrin
 - Inhibits adhesion to MAdCAM-1 and fibronectin, but not VCAM-11
- Contains a mutated Fc region, preventing elicitation of²
 - Complement-mediated cytotoxicity
 - Antibody-dependent cellular cytotoxicity
 - Cytokine release

Fc, fragment crystallizable; mAb, monoclonal antibody; VCAM-1, vascular cell adhesion molecule-1.
1. Soler D, et al. *J Pharmacol Exp Ther* 2009;330:864–75; 2. Data on file.

Vedolizumab: clinical trial data

Phase 3 trials

Size	Arms	Primary endpoint(s)	Trial start	Completion
Ulcerative colitis				
826 ¹ (GEMINI I)	<ul style="list-style-type: none"> • Induction: vedolizumab or placebo at weeks 0, 2, 6 • Maintenance: vedolizumab Q4W or Q8W, or placebo Q4W 	<ul style="list-style-type: none"> • Clinical response at Week 6 • Clinical remission at Week 52 	Jan 2009	Jul 2012
Crohn's Disease				
1,059 ² (GEMINI II)	<ul style="list-style-type: none"> • Induction: vedolizumab or placebo at weeks 0, 2, 6 • Maintenance: vedolizumab Q4W or Q8W, or placebo Q4W 	<ul style="list-style-type: none"> • Clinical remission at Weeks 6 and 52 	Dec 2008	Oct 2012
416 ³ (GEMINI III)	<ul style="list-style-type: none"> • Induction: vedolizumab or placebo at weeks 0, 2, 6 	<ul style="list-style-type: none"> • Clinical remission in the anti-TNF therapy subpopulation at Week 6 	Nov 2010	Apr 2012
Safety				
2,200 ⁴ (GEMINI LTS)	<ul style="list-style-type: none"> • Open-label vedolizumab Q4W 	<ul style="list-style-type: none"> • Safety, IBD-related events and QoL up to week 100 	May 2009	Aug 2016

1. Feagan et al. *N Engl J Med* 2013;369:699–710.
2. Sandborn WJ et al. *N Engl J Med* 2013;369:711–21.
3. Sands B et al. UEGW 2013, DDW 2014.
4. NCT00790933 clinicaltrials.gov.

GEMINI II: vedolizumab in CD induction at Week 6

Induction ITT population

Sandborn WJ et al. *N Engl J Med* 2013;369:711-21.

GEMINI II: vedolizumab in CD maintenance at Week 52

Maintenance ITT population

*p<0.05; **p<0.01

†CS tapering began in responders at 6 weeks; for others, as soon as a clinical response was achieved.

Sandborn WJ et al. *N Engl J Med* 2013;369:711-21.

GEMINI III: vedolizumab induction therapy for CD and prior anti-TNF failure

- Phase 3, multicentre, prospective, RCT (N=315)
- Randomised 3:2, patients received VDZ 300mg (IV) or PBO on days 1 & 15
- Rates of AEs and serious AEs were similar between VDZ and PBO groups

Sands B, et al. Gastroenterology 2014

GEMINI II: adverse events affecting ≥5% of VDZ-treated patients during maintenance phase, safety population

Preferred term , N (%)	Placebo N=301	VDZ N=814
CD	65 (22)	164 (20)
Arthralgia	40 (13)	110 (14)
Pyrexia	40 (13)	103 (13)
Nasopharyngitis	24 (8)	100 (12)
Headache	47 (16)	97 (12)
Nausea	30 (10)	90 (11)
Abdominal pain	39 (13)	79 (10)
Upper respiratory tract infection	17 (6)	54 (7)
Fatigue	14 (5)	53 (7)
Vomiting	23 (8)	49 (6)
Back pain	12 (4)	38 (5)
Any serious AE*	46 (15)	199 (24)

CD, Crohn's disease.

*CD (n=21 [7%] and 99 [12%] for placebo and VDZ, respectively) and anal abscess (n=1 [1%] and 16 [2%]); all other serious AEs occurred in ≤1% of patients in each group.

Sandborn WJ et al. N Engl J Med 2013;369:711-21.

GEMINI I: vedolizumab induction therapy for UC at Week 6

Week 6 outcomes after 2-dose induction

Primary endpoint

- Phase 3, multicentre, prospective, RCT (N=374)
 - Randomised 3:2, patients received VDZ 300mg (IV) or PBO on days 1 & 15
- Mod-to-severe active UC (Mayo 8.6, mean), despite conventional therapy
 - UC diagnosis ~6.4 yrs, CS (~54%), IS (~31%) and anti-TNF failures (~39%)
- Rates of AEs and serious AEs were similar between VDZ and PBO groups

AE, adverse event; CS, corticosteroid; IS, immunosuppressant; RCT, randomised controlled trial.

Feagan BG, et al. *N Eng J Med* 2013; 369:699-710.

GEMINI I: vedolizumab induction therapy for UC at Week 6

Week 6 outcomes after 2-dose induction by TNF antagonist-status

Feagan BG, et al. *N Eng J Med* 2013; 369:699-710.

GEMINI I: vedolizumab in UC maintenance at Week 52

Primary and secondary efficacy endpoints

Feagan BG, et al. N Eng J Med 2013; 369:699-710.

GEMINI I: vedolizumab in UC maintenance at Week 52

Clinical remission/durable clinical response by anti TNF antagonist-status

Feagan BG, et al. N Eng J Med 2013; 369:699-710.

GEMINI I:
adverse events affecting $\geq 5\%$ of VDZ-treated patients
during maintenance phase, safety population

Preferred term, N (%)	Placebo N=275	VDZ N=620
Colitis ulcerative	58 (21)	97 (16)
Headache	28 (10)	80 (13)
Nasopharyngitis	26 (9)	80 (13)
Arthralgia	25 (9)	56 (9)
Upper respiratory tract infection	21 (8)	52 (8)
Nausea	19 (7)	38 (6)
Cough	13 (5)	36 (6)
Anemia	16 (6)	35 (6)
Abdominal pain	10 (4)	35 (6)
Fatigue	10 (4)	33 (5)
Influenza	6 (2)	30 (5)
Any serious AE	37 (13)	77 (12)

AE, adverse event.

Feagan BG, et al. *N Engl J Med* 2013;369:699-710.

PML risk assessment

- >3000 patients treated with vedolizumab
 - >2400 with prior/concomitant immunosuppressant exposure
 - >900 with over 24 months of exposure
 - >50% presumed seropositive for JC virus
- No cases of PML have been observed in patients receiving vedolizumab

Sandborn WJ et al. *N Engl J Med* 2013;369:711-21

Phase II: safety and efficacy of etrolizumab (humanised anti- $\beta 7$ mAb) for moderate-to-severe UC

Week 10 clinical and endoscopic outcomes (all comers)

- Phase 2, multicentre, prospective, RCT (N=119)
 - Randomised 1:1:1, patients received ETZ 100 mg/mo s.c. or 420 mg loading dose between Week 0 & 2 then 300 mg/mo s.c. or PBO for 3 doses
- Moderate-to-severe active UC: Mayo ≥ 5 , endoscopy subscore ≥ 2 and RBS ≥ 1
- UC diagnosis ~ 9 yrs, mean Mayo ~ 9 , CS ($\sim 42\%$), IS ($\sim 38\%$), anti-TNF failures ($\sim 60\%$)
- Rates of AEs were comparable between ETZ and PBO groups

ETZ, etrolizumab; RBS, rectal bleed severity.
Clinical remission: Mayo score ≤ 2 with no individual score > 1 .
Clinical trial gov: NCT01336465

Vermeire S, et al. Lancet 2014, in press

Other promising targets

Ustekinumab in moderate-to-severe Crohn's disease

- Overall results
- IFX experienced-patients

Sandborn WJ et al Gastroenterology 2008;135:1130-1141

CERTIFI: Ustekinumab in anti-TNF alpha resistant Crohn's Disease (Induction Phase)

Primary endpoint

Clinical response
(>100-point CDAI decrease)

Clinical remission

Sandborn WJ, et al. N Engl J Med 2012

CERTIFI: Ustekinumab in anti-TNF alpha resistant Crohn's Disease (Maintenance Phase)

*: $p < 0.05$

Sandborn WJ, et al. N Engl J Med 2012

Phase III studies evaluating ustekinumab in Crohn disease

Study	Description	Study end point	Status
UNITI-1 ¹⁴	Randomized placebo-controlled trial evaluating ustekinumab in moderate-to-severely active CD with prior failure or intolerance to anti-TNF α therapy	Clinical response, week 6	Completed, results pending
UNITI-2 ¹⁵	Randomized placebo-controlled trial evaluating ustekinumab in moderate-to-severely active CD without prior failure or intolerance to anti-TNF α therapy	Clinical response, week 6	Recruiting
IM-UNITI ¹⁶	Randomized placebo-controlled trial evaluating safety and efficacy of ustekinumab in CD patients with clinical response in UNITI-1 or UNITI-2	Clinical remission, week 44	Recruiting

Tuskey A et al Clinical and Experimental Gastroenterology 2014;7:173-179

Tofacitinib, an oral Janus Kinase inhibitor, in active UC

194 active UC (Mayo ≥ 6), 8-week treatment

double-blind, placebo-controlled, phase 2 trial

Sandborn W et al. NEJM 2012