2019. PANTS

Observ/ antiTNF/CD/ Failure

Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal CD: a prospective, multicentre, cohort study

AntiTNF naïve patients started treatment with ADA or IFX. Evaluated for 54w or until drug withdrawal

Outcomes: primary non-response w14; non remission w54; adverse events leading to drug withdrawal

Results:

- Primary non-response related to: low drug levels w14.
- Non-Remission related to: Optimal w14 drug levels were 7mg/L IFX and 12mg/L ADA. Smoking and obesity related with treatment failure.

Conclusions:

Anti-TNF treatment failure is common and is predicted by low drug concentrations, mediated in part by immunogenicity.

	Infliximab		Adalimumab		Both drugs	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Week 14						
Primary non-response	170/775	21·9% (19·1–25·0)	125/466	26·8% (22·9–31·1)	295/1241	23·8% (21·4–26·2)
Grey zone	154/775	19·9% (17·1–22·9)	83/466	17·8% (14·4–21·6)	237/1241	19·1% (16·9–21·4)
Response	122/775	15·7% (13·2–18·5)	61/466	13·1% (10·2–16·5)	183/1241	14·7% (12·8–16·8)
Remission	329/775	42·5% (38·9–46·0)	197/466	42·3% (37·7–46·9)	526/1241	42·4% (39·6–45·2)
Week 54						
Non-remission	469/770	60·9% (57·4–64·0)	295/441	66·9% (62·3–71·3)	764/1211	63·1% (60·3–65·8)
Remission	301/770	39·1% (35·6–42·6)	146/441	33·1% (28·7–37·7)	447/1211	36·9% (34·2–39·7)
Adverse event curtailing treatment (not including exacerbation of Crohn's disease)	84/995	8·8% (7·1–10·8)	42/655	6·4% (4·7–8·6)	126/1610	7·8% (6·6–9·2)

Table 2: Key outcomes at weeks 14 and week 54

	Infliximab		Adalimumab	
	OR*, fold-change†, or HR‡ (95% CI)	p value	OR*, fold-change†, or HR‡ (95% CI)	p value
Primary non-response at week 14*				
Baseline immunomodulator	0·71 (0·44–1·13)	0·14	–	–
Log_{10} (week 14 drug concentration [mg/L])	0·35 (0·20–0·62)	0·00038	0·13 (0·06–0·28)	<0·0001
Baseline BMI category				
Normal	–	–	1 (ref)	–
Underweight	–	–	0·36 (0·07–1·20)	0·13
Overweight	–	–	0·63 (0·34–1·15)	0·14
Obese	–	–	1·57 (0·82–2·99)	0·17
Week 54 non-remission*				
Sex				
Male	0·68 (0·45–1·02)	0·063	–	–
Female	1 (ref)	1 (ref)	–	–
Age at first dose (years)	1·01 (1·00–1·03)	0·11	–	–
History of perianal disease	0·60 (0·35–1·04)	0·070	0·29 (0·09–0·85)	0·029
Baseline BMI category				
Normal	1 (ref)	–	1 (ref)	–
Underweight	0·92 (0·51–1·65)	0·79	1·20 (0·40–3·57)	0·74
Overweight	1·73 (1·02–2·99)	0·045	2·31 (1·28–4·25)	0·0059
Obese	1·99 (0·98–4·17)	0·062	3·42 (1·51–8·43)	0·0046
Baseline white cell count (x 10^9 cells per L)	1·05 (0·99–1·12)	0·12	–	–
Log_{10} (week 14 drug concentration [mg/L])	0·29 (0·16–0·52)	<0·0001	0·03 (0·01–0·12)	<0·0001
Immunogenicity in first year				
Antibody negative	1 (ref)	–	–	–
Antibody negative, detectable drug concentration	0·77 (0·48–1·22)	0·27	–	–
Antibody positive, undetectable drug concentration	1·64 (0·95–2·85)	0·079	–	–
Smoker at baseline	–	–	2·27 (1·13–4·81)	0·025
Week 14 drug concentration†				
Log_{10} (baseline faecal calprotectin [µg/g])	0·81 (0·68–0·98)	0·028	–	–
Week 14 drug concentration†				
Log_{10} (baseline faecal calprotectin [µg/g])	0·81 (0·68–0·98)	0·028	–	–
Smoker at baseline	0·78 (0·61–0·99)	0·045	0·89 (0·77–1·03)	0·12
Log_{10} (week 14 anti-drug antibody concentration [mg/L])	0·50 (0·42–0·60)	<0·0001	0·40 (0·35–0·45)	<0·0001
Log_{10} (week 14 CRP [mg/L])	0·74 (0·62–0·88)	0·00075	–	–
Week 14 albumin (g/L)	1·03 (1·01–1·05)	0·00018	–	–
Log_{10} (week 14 faecal calprotectin [µg/g])	0·74 (0·63–0·88)	0·00057	0·72 (0·66–0·79)	<0·0001
Baseline BMI category				
Normal	–	–	1 (ref)	–
Underweight	–	–	1·07 (0·84–1·36)	0·57
Overweight	–	–	0·88 (0·78–1·00)	0·056
Obese	–	–	0·71 (0·60–0·83)	<0·0001
Baseline HBI or sPCDAI remission	–	–	1·14 (1·02–1·28)	0·021
Log_{10} (baseline CRP [mg/L])	–	–	0·91 (0·82–1·00)	0·056
Week 54 drug concentration†				
Baseline immunomodulator	1·27 (1·02–1·59)	0·034	–	–
Baseline BMI category				
Normal	1 (ref)	–	1 (ref)	–
Underweight	0·80 (0·62–1·04)	0·092	1·02 (0·80–1·30)	0·85
Overweight	0·79 (0·62–1·00)	0·048	0·88 (0·77–0·99)	0·041
Obese	0·95 (0·67–1·35)	0·77	0·73 (0·63–0·85)	<0·0001
Log_{10} (week 14 anti-drug antibody concentration [mg/L])	0·73 (0·58–0·92)	0·0087	0·40 (0·35–0·44)	<0·0001
Log_{10} (week 14 CRP [mg/L])	0·88 (0·72–1·07)	0·19	–	–
Log_{10} (week 14 faecal calprotectin [µg/g])	0·74 (0·62–0·89)	0·00099	0·72 (0·66–0·79)	<0·0001
Week 14 HBI or sPCDAI remission	–	–	1·25 (1·10–1·41)	0·00066
Smoker at baseline	–	–	0·90 (0·79–1·04)	0·16
Immunogenicity‡				
Disease duration	0·99 (0·98–1·01)	0·32	–	–
Baseline immunomodulator	0·39 (0·32–0·48)	<0·0001	0·47 (0·32–0·67)	<0·0001
Baseline BMI category				
Normal	1 (ref)	–	1 (ref)	–
Underweight	1·29 (0·99–1·69)	0·060	1·26 (0·60–2·67)	0·54
Overweight	0·94 (0·74–1·20)	0·61	1·08 (0·70–1·67)	0·73
Obese	1·27 (0·96–1·67)	0·090	2·23 (1·44–3·46)	<0·0001
Current smoker	1·42 (1·12–1·81)	0·0045	–	–
Immunogenicity (excluding patients with immunogenicity or censored before week 14)				
Baseline immunomodulator	0·57 (0·43–0·75)	<0·0001	0·39 (0·22–0·69)	0·0011
Smoker at baseline	1·88 (1·35–2·62)	0·00021	–	–
Log_{10} (week 14 drug concentration [mg/L])	0·43 (0·30–0·61)	<0·0001	0·05 (0·02–0·14)	<0·0001

BMI=body-mass index. CRP=C-reactive protein. HBI=Harvey-Bradshaw index. sPCDAI=Short Paediatric Crohn's Disease Activity Index. *ORs (95% CI) and p values were calculated using logistic regression for week 14 primary non-response and week 54 non-remission. †For drug concentration, models were calculated using linear regression of the log-transformed drug concentration, with exponentiated β values expressed here as fold changes (95% CI). ‡For immunogenicity, models were generated using Cox proportional hazards and coefficients expressed as hazard ratios (HRs [95% CI]).

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