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EDITORIAL

Defining and predicting deep remission in patients with perianal fistulizing Crohn's disease on anti-tumor necrosis factor therapy

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Abstract

Perianal fistulas can occur to up to one-third of patients with Crohn's disease (CD) leading to significant disabling disease and morbidity. Fistulising perianal CD treatment often necessitates a combined pharmacological and surgical approach. Anti-tumor necrosis factor (anti-TNF) therapy, particularly infliximab, has been shown to be very effective for both perianal and internal fistulising CD. Nevertheless, current data suggest that sustained remission and long-term complete fistula healing can be achieved in only 30% to 50% of patients. Moreover, these percentages refer mostly to clinical rather than deep remission, defined as endoscopic and radiologic remission, which is quickly emerging as the preferred goal of therapy. Unfortunately, the therapeutic options for perianal fistulising CD are still limited. As such, it would be of great value to be able to predict, and more importantly, prevent treatment failure in these patients by early and continued optimization of anti-TNF therapy. Similar to ulcerative colitis and luminal CD, recent data demonstrate that higher infliximab concentrations are associated with better clinical outcomes in patients with perianal fistulising CD. This suggests that therapeutic drug monitoring and a treat-to-trough therapeutic approach may emerge as the new standard of care for optimizing anti-TNF therapy in patients with perianal fistulising CD.

Key words: Inflammatory bowel disease; Infliximab; Adalimumab; Magnetic resonance imaging; Drug monitoring; Fistula healing

Core tip: Defining and predicting deep remission is important to guide the management of patients with perianal fistulizing Crohn's disease (CD). Deep remission, defined as complete fistula healing based on objective endoscopic and radiologic findings, should be the goal of care in the treatment of patients with perianal CD. Currently, anti-tumor necrosis factor (anti-TNF) are the standard of care for perianal CD, but long-term outcomes are disappointing. Data suggests that higher infliximab concentrations are associated with better clinical outcomes in patients with perianal fistulising CD and thus therapeutic drug monitoring may be a valid therapeutic strategy for optimizing anti-TNF therapy towards improved objective outcomes and deep remission.

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INTRODUCTION

Perianal fistulas can develop to up to one-third of patients with Crohn's disease (CD) leading to disabling disease, morbidity, and a significant impairment in quality of life[1]. The treatment of fistulising perianal CD is not simple and often requires a multidisciplinary approach of both pharmacological and surgical therapy especially for complex perianal fistulae[2]. Anti-tumor necrosis factor (anti-TNF) therapy has revolutionized the treatment of both perianal and internal fistulising CD[3-18]. Nevertheless, therapeutic outcomes from randomised controlled trials (RCTs), post-hoc analyses of RCTs and real-life prospective or retrospective studies show that long-term remission can be achieved in only 30%-50% of patients (Table 1). Moreover, these percentages refer mostly to clinical remission, based on symptoms and physician global assessment (PGA), and not to objective endoscopic and/or radiological healing. At this time, the preferred goal of treatment should be deep remission, or the combination of clinical and the more objective measures, including radiologic and endoscopic healing. As therapeutic options for perianal fistulising CD are still limited it is very important to attempt to predict and subsequently prevent treatment failure in these patients. Preliminary data demonstrate that higher infliximab concentrations are associated with improved clinical outcomes in patients with perianal fistulising CD, suggesting that therapeutic drug monitoring (TDM) and a treat-to-trough approach is likely a valid therapeutic strategy for optimizing anti-TNF therapy in these patients[19,20].

Defining deep remission

Most studies typically use clinical remission, defined as absence of any draining fistulas based on PGA and patients' reports, as a therapeutic endpoint for perianal fistulising CD[3-18]. Nevertheless, deep remission, defined as mucosal and/or radiological healing of fistulas, is likely a more appropriate goal of therapy for perianal fistulising CD. T2-weighted magnetic resonance imaging (MRI) with fat-suppression is considered the gold-standard for fistula imaging and an MRI-based score is currently available for defining disease activity, although it is still not widely used in clinical practice[1]. Thomassin *et al*[11] have recently showed that deep remission, defined as a composite clinical (absence of any draining fistulas and self-reported drainage episodes by the patient at two successive evaluations), endoscopic (absence of ulcers in the anal canal) and radiological (absence of T2 hyperintensity and contrast enhancement on MRI) remission, was achieved in approximately one-third of patients with perianal fistulizing CD[11].

Predicting deep remission

As new drugs for the treatment of perianal fistulising CD are still awaited, it is important to be able to predict who will achieve deep remission and who will not respond adequately to typical anti-TNF dosing and will require early (and continued) optimization[1,2]. Although several variables have been associated with improved outcomes (Table 2), prediction of deep remission remains a challenge. Thomassin *et al*[11] have recently identified absence of rectal involvement on MRI (OR = 4.6; 95%CI: 1.03-20.5) as the only variable associated with deep remission in patients with perianal fistulizing CD[11]. Similar to ulcerative colitis and luminal CD[19-25], recent data demonstrate that higher infliximab concentrations are associated with better clinical outcomes in patients with perianal fistulising CD[26,27]. Regarding maintenance therapy Yarur *et al*[26] recently showed that infliximab trough concentrations $\geqslant$ 10.1 μg/mL are associated with fistula healing and based on quartile analyses proposed that physicians should aim for even higher concentrations (> 20.2 μg/mL) before giving up and moving on to alternative therapies with a different mechanism of action.

CONCLUSION

Deep remission defined as a composite clinical, endoscopic and radiological remission should really be considered the goal of therapy in patients with perianal fistulizing CD. TDM may be a valid therapeutic strategy for optimising anti-TNF therapy, improving therapeutic outcomes, and moving towards more personalized medical care.

Table 1 Long-term outcomes of patients with perianal fistulizing Crohn's disease on anti-tumor necrosis factor maintenance therapy

Type of anti-TNF therapy	*n*	Complex fistulas, %	Follow up, wk	Therapeutic outcome of interest	Therapeutic outcome, %	Ref.
IFX	68	75	52	Complete fistula closure & CDAI < 150	34	[4]
IFX	59	85	> 56	Complete fistula closure (PGA)	41	[5]
IFX	13	ND	95[1]	Reduction of fistulas number (MRI)	15	[5]
IFX	156	82	250[1]	At least 1 fistula closure	69	[6]
IFX	12	ND	156	Clinical remission (PGA)	33	[7]
IFX	12	ND	156	Radiological healing (MRI)	42	[7]
IFX	19	ND	52	Absence of draining fistulas (PGA)	53	[8]
IFX	26	69	255[2]	Complete fistula closure	42	[9]
IFX (RCT)	96	ND	54	Complete fistula closure	36	[10]
IFX/ADM	49	ND	160[2]	Deep remission (PGA, MRI, endoscopy)	33	[11]
IFX/ADM	49	ND	160[2]	Absence of draining fistulas (PGA)	53	[11]
IFX/ADM	20	ND	52	Absence of draining fistulas (PGA)	35	[12]
IFX/ADM	78	67	192[1]	Absence of drainage with seton removal	53	[13]
IFX/ADM	20	ND	78	Radiological healing (MRI)	30	[8]
ADM	7	ND	156	Absence of draining fistulas (PGA)	0	[7]
ADM	7	ND	156	Radiological healing (MRI)	14	[7]
ADM	7	ND	52	Absence of draining fistulas (PGA)	29	[8]
ADM	39	ND	52	Clinical remission (FDAI)	41	[14]
ADM	14	ND	52	Radiological healing (MRI)	43	[14]
ADM	53	ND	40	Complete fistula closure	41	[15]
ADM (RCT)	70	ND	56	Absence of draining fistulas (PGA)	33	[16]
ADM (post hoc)	70	ND	116	Absence of draining fistulas (PGA)	31	[17]
CZP (RCT)	28	ND	26	Complete fistula closure	36	[18]

[1]Median; [2]Mean. CDAI: Crohn's disease activity index; TNF: Tumor necrosis factor; ADM: Adalimumab; IFX: Infliximab; CZP: Certolizumab pegol; RCT: Randomized controlled trial; PGA: Physician global assessment; ND: Not defined; FDAI: Fistula drainage assessment index; MRI: Magnetic resonance imaging.

Table 2 Variables associated with improved therapeutic outcomes of anti-tumor necrosis factor maintenance therapy in patients with perianal fistulizing Crohn's disease

Variables	Ref.
Clinical or phenotypic	
Ileocolonic disease	[6]
Concomitant immunosuppressants	[6]
Duration of seton drainage (< 34 wk)	[6]
Duration of infliximab treatment (> 118 wk)	[6]
Number of infliximab infusions (> 19)	[6]
Absence of complex fistulas	[14]
Male gender	[26]
Absence of switch of anti-TNF therapy	[11]
Imaging	
Absence of persisting fistulas on MRI	[5]
Absence of collections at baseline on MRI	[5]
Absence of rectal wall involvement on MRI	[5]
Absence of single-branched fistulas on MRI	[5]
Absence of rectal involvement on MRI	[11]
Serologic	
Infliximab (maintenance) trough concentrations ⩾ 10.1 μg/mL	[26]
Endoscopic	
Absence of active proctitis	[11]

TNF: Tumor necrosis factor; MRI: Magnetic resonance imaging.

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