Journal of Crohn's and Colitis, 2015, 982–987
doi:10.1093/ecco-jcc/jjv159
Advance Access publication September 8, 2015
Original Article

Original Article

Association Between Infliximab Trough Levels and the Occurrence of Paradoxical Manifestations in Patients with Inflammatory Bowel Disease: a Case-Control Study

C. Coutzac,[a] J. Chapuis,[a] F. Poullenot,[a] E. Chabrun,[a] M. Capdepont,[a] P. Blanco,[b] D. Laharie[a]

[a]Service d'Hépato-gastroentérologie, CHU de Bordeaux, Hôpital Haut-Lévêque, Pessac, France [b]Laboratoire d'immunologie, CHU de Bordeaux, Hôpital Pellegrin, Bordeaux, France

Corresponding author: David Laharie, MD, Service d'Hépato-gastroentérologie, CHU de Bordeaux, Hôpital Haut-Leveque, Pessac, F-33600 France. Tel.: +33 557 656 438; fax: +33 557 656 445; email: david.laharie@chu-bordeaux.fr

Abstract

Background and Aim: Anti-tumour necrosis factor [TNF] agents have dramatically improved the prognosis of inflammatory bowel disease [IBD]. However, despite their good safety profile, use of these agents may lead to paradoxical manifestations involving skin or joints. Pathogenesis of such side effects is poorly understood and may involve anti-TNF pharmacokinetics. The aim of the present study was to look for an association between infliximab trough levels [ITL] and cutaneous [CPM] or rheumatological [RPM] paradoxical manifestations.

Methods: IBD patients receiving infliximab as maintenance therapy were included in a cross-sectional prospective monocentre study. At inclusion, patients had an ITL measurement [LISA-TRACKER®, Biomedical Diagnostics BMD] and were assessed for paradoxical manifestations: a CPM was defined by new onset or exacerbation of pre-existing psoriasis lesions during IFX therapy, and an RPM by new onset of severe poly-arthralgia during IFX therapy.

Results: Among the 121 patients included [69 female; median age: 38.9 years; 92 with Crohn's disease], 7% had CPM and 8% RPM. Median ITL values were 5.87 [range: 0.52–19.53] µg/ml in patients with CPM and 1.90 [0.00–13.5] µg/ml in those with RPM, as compared respectively with 5.12 [0.00–49.12] µg/ml in patients without CPM [$p = 0.56$] and 5.57 [0.00–49.12] µg/ml in those without RPM [$p = 0.058$]. No prognostic factor was associated with CPM. The single factor associated with RPM was elevated antinuclear antibodies.

Conclusion: ITL were not elevated in IBD patients developing cutaneous or rheumatological paradoxical manifestations when receiving IFX as maintenance therapy. As suggested by the high level of antinuclear antibodies, RPM could be related to an induced autoimmune disorder.

Keywords: Infliximab; inflammatory bowel disease; infliximab trough level; Crohn's disease; ulcerative colitis; psoriasis; paradoxical manifestations

1. Introduction

Infliximab [IFX] is a chimeric monoclonal anti-tumour necrosis [TNF] alpha antibody used over more than 15 years in many inflammatory disorders such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease [IBD]. In Crohn's disease [CD] and ulcerative colitis [UC] patients, IFX has widely demonstrated its

efficacy, inducing and maintaining remission, closing fistulas, healing gut mucosa and, reducing surgery and hospitalizations.[1,2,3,4,5,6]

IFX safety has been scrutinised through controlled trials[4] and cohort studies.[7,8] Most common side effects are drug-related immunogenicity [acute infusion reactions or delayed hypersensitivity reactions],[9] and infections related to immunosuppression [viral, bacterial, parasitic, and opportunistic infections].[10] No increased risk of cancer has been identified so far except a few cases of hepatosplenic T-cell lymphoma in patients receiving an associated thiopurine[11] and a possible mild increase of melanoma.[12]

New onset and exacerbation of auto-immune disorders have also been reported in IBD patients receiving IFX: demyelination, cutaneous lesions,[13] and joint pain.[14] Surprisingly, new onset or exacerbations of psoriasis or inflammatory rheumatisms have been observed in patients treated with IFX although this drug has demonstrated its efficacy in these two autoimmune disorders. Therefore, such manifestations arising under IFX have been called paradoxical.[14,15,16] Cutaneous paradoxical manifestations [CPM] are observed in 10–20% of IBD patients receiving IFX.[7,17,18,19,20] They are characterised by psoriasiform and/or eczematiform lesions, usually located on palms, soles, and scalp. Patients can also develop new-onset severe arthralgia under anti-TNF therapy, in spite of having no previous rheumatological symptoms before starting treatment.[21] These rheumatological paradoxical manifestations [RPM], described in the Leuven cohort, are not considered to be associated with the underlying IBD.[21] This entity, not well characterised, is usually associated with detectable antinuclear antibodies [ANA] suggesting a lupus-like reaction.[22] Pathogenesis of CPM and RPM remains poorly understood[23,24] and may also involve IFX pharmacokinetics. Therefore, the aim of the present study was to compare IFX pharmacokinetics in IBD patients developing or not developing CPM or RPM.

2. Patients and Methods

2.1. Study design

This was a cross-sectional, monocentre, case-control study conducted in the gastroenterology unit of the University Hospital of Haut-Leveque, Pessac, France, from May 2010 to January 2011.

All consecutive patients were prospectively recruited according to the following criteria: diagnosis of IBD established by the combination of medical history, clinical evaluation, laboratory data [including negative stool examinations for infectious agents], and typical endoscopic, histological and radiological findings according to ECCO statements,[25,26] receiving maintenance therapy with IFX at whatever interval and dosage. Patients treated with another biological agent or receiving IFX for extra-intestinal manifestations were excluded from the study. Inclusion date corresponded to the first IFX infusion given as maintenance regimen, ie from Week 14 during the study period.

At inclusion, patients were assessed for CPM and RPM as follows: CPM was defined by induction of new-onset lesions or exacerbation of pre-existing psoriasis with or without morphological differences, during IFX therapy, confirmed by a dermatologist as a paradoxical manifestation; RPM was defined by new onset of severe polyarthralgia in patients without any previous rheumatological manifestation before starting IFX, confirmed by a rheumatologist as a paradoxical manifestation. To rule out any previous undiagnosed inflammatory rheumatism related to IBD, patients having severe polyarthralgia before starting IFX were not considered as having RPM. For the present study, CPM and RPM were considered when they were significantly affecting the patient's quality of life and/or requiring local or systemic treatment.

At inclusion, before administering IFX, blood samples for IFX trough levels [ITL] and antibodies to infliximab [ATIs] assays were collected just before the IFX infusion and frozen at -20°C. All the plasma assays were measured at the same time [ITL and ATI dosages were performed by LISA-TRACKER® Premium Infliximab LTI001®, Biomedical Diagnostics BMD Society], blinded to clinical findings.

2.2. Data collection

Data were collected from patient's medical files. The following baseline characteristics were recorded: date of birth, gender, disease duration, age at diagnosis, IBD subtype [CD, UC or indeterminate colitis], disease localisation and behaviour according Montreal classification,[27] perianal disease, smoking history, extra-intestinal manifestations including previous history of psoriasis and inflammatory rheumatism before starting IFX therapy, previous history of intestinal or perianal surgery, past and current treatment [steroids, biological, and conventional immunosuppressants such as thiopurine, methotrexate, and cyclosporin], current IFX maintenance regimen with total number of infusions, frequency, and dosing, IFX efficacy [see below], C-reactive protein [CRP] level [mg/l], ANA level [positive if higher than 1/100], ITL [µg/ml] and, if positive, anti-DNA antibodies level [positive if higher than 29.90 UI/ml] and ATI levels [positive if more than 10 ng/ml].

IFX efficacy was assessed at inclusion by the Harvey Bradshaw index[28] for CD [remission defined by a score less than 5 points, response by a score between 5 and 12 with a decrease from the beginning of the treatment and failure], and by the partial Mayo score[29] for UC [clinical remission defined by score less than 3 points with no individual subscore exceeding 1 point, clinical response by a score decrease of at least 3 points from the beginning of the treatment and failure]. An optimised IFX regimen was not considered as treatment failure.

2.3. Outcomes

Objectives were i] to compare median ITL values between cases and controls for each type of paradoxical manifestation [cases were patients with CPM or RPM and controls were those without CPM or RPM]; ii] to compare proportions of patients ATI-positive according to occurrence of CPM or RPM; and iii] to look for associated factors with each paradoxical manifestation.

2.4. Statistics

Continuous variables are presented as medians and range; categorical variables are presented as percentages. Continuous data were analysed using the Mann-Whitney test. Categorical data were analysed using the Pearson chi-square test or Fisher's exact test if any cell number was < 5, for frequencies. Mann-Whitney testing was performed to compare median ITL and ATI in cases and controls.

Univariate and multivariate analyses of associated factors with CPM or RPM was performed. For each paradoxical manifestation, the following variables were analysed: sex, age, IBD subtype [CD, UC, or indeterminate colitis], smoking history, disease localisation and behaviour according Montreal classification,[27] current treatment [conventional immunosuppressants such as thiopurine, methotrexate, and cyclosporin], current IFX maintenance regimen with total number of infusions, frequency ,and dosing, IFX efficacy, antinuclear antibodies level [positive if higher than 1/100],

ITL [µg/ml], and ATI levels [positive if more than 10 ng/ml]. A logistic regression model was created using associated variables with *p*-value below 0.10. Odds ratios [OR] were determined in the model for variables that remained significant [$p < 0.05$]. Two-sided statistical tests were used for all analyses; $p < 0.05$ was considered significant.

3. Results

3.1. Patient's characteristics

During the study period, 137 consecutive IBD patients received IFX in the unit. Among them, 16 patients were excluded from the analysis: three patients receiving IFX for extra-intestinal manifestations, one with no available dosage, and 12 receiving an IFX induction regimen. Therefore, 121 patients were included and analysed.

The main characteristics at inclusion of the 121 included patients are given in Table 1. To summarise, 69 [57%] were female and median age was 38.9 years [range: 16.3–80.9]. IBD subtypes were the following: 92 [76%] CD, 27 [22%] UC, and 2 [2%] indeterminate colitis. Median age at diagnosis was 27.2 years [11.5–74.0]. Five [4%] patients had history of previous dermatological disorders [four cases of psoriasis and one of eczema] and 16 [13%] had history of associated inflammatory rheumatism. In all, 25 [21%] patients received an associated conventional immunosuppressant which was thiopurine in all cases. Median number of IFX infusions as maintenance was 15 [2–54]. Considering the IFX maintenance regimen, 65 [54%] patients received the conventional dose [5 mg/kg/8 weeks] and the 56 others [46%] an optimised regimen.

Table 1. Main characteristics at baseline of the 121 patients receiving infliximab as maintenance therapy.

Variable	
Female gender, *n* [%]	69 [57]
Median age, in years [range]	38.9 [16.3–81.9]
Active smoking, *n* [%]	24 [20]
Previous dermatological disease, *n* [%]	5 [4]
Previous inflammatory rheumatism, *n* [%]	16 [13]
IBD subtype, *n* [%]	
Crohn's disease	92 [76]
Ulcerative colitis	27 [22]
Indeterminate colitis	2 [2]
Disease location	
Crohn's disease: L1	10 [11]
L2	21 [22]
L3	52 [55]
L4	11 [12]
Ulcerative colitis: E1	1 [4]
E2	10 [37]
E3	16 [59]
Associated immunosuppressant, *n* [%]	25 [21]
Infliximab maintenance regimen, *n* [%]	
5 mg/kg/8 weeks	65 [54]
Other	56 [46]
Median number of previous infusions [range]	15 [2–54]
Clinical efficacy of infliximab, *n* [%]	
Remission	88 [73]
Response	28 [23]
Failure	5 [4]
Median infliximab trough levels in µg/ml [range]	5.18 [0–49.12]
ATI-positive, *n* [%]	16 [13]
ANA-positive [> 1/100], *n* [%]	67 [55]

IBD, inflammatory bowel disease; ATI, antibodies to infliximab; ANA, antinuclear antibodies.

At inclusion, the median ITL level was 5.18 µg/ml [range: 0.00–49.12] in the whole population, 16 [13%] patients were ATI positive [10-15 962 ng/ml], and 67 [55%] were antinuclear antibody positive.

3.2. Cutaneous paradoxical manifestations

Among the 121 patients recruited, nine [7%] patients presented CPM at inclusion: eight had psoriatic or eczema skin lesions and one a lymphocytic vasculitis. All except one were female and eight had CD. Median age at inclusion was 26 years [range: 18–33] and two patients [22%] were active smokers. Three patients with CPM [33%] had a previous history of psoriasis [$n = 2$] or eczema [$n = 1$] before starting IFX.

Skin lesions were distributed in single [$n = 3$] or multiple [$n = 6$] sites. The most frequently affected areas were flexures [$n = 3$] or palms and soles [$n = 3$]. One patient developed psoriatic lesions on the scalp [Figure 1]. The usual psoriatic locations were involved in three patients [sacralis area in two and the extensor surfaces of elbows and knees in one]. No nail involvement was observed. One patient developed a lymphocytic vasculitis with nodulation in the fingers, confirmed by biopsy.

Concerning treatments given for IBD, IFX was associated with a conventional immunosuppressant in three patients. The median number of IFX infusions at the date of inclusion was 19 [8–31] and six patients had received more than 15 infusions. At inclusion, eight patients were in clinical remission and one was a responder to IFX.

In the nine subjects with CPM related to IFX, ITL median value was 5.87 µg/ml [0.52–19.53], as compared with 5.12 µg/ml [0.00–49.12] in the 112 remaining patients [$p = 0.560$] [Figure 2]. All patients with CPM were ATI negative [< 10 ng/ml], as compared with 16/112 patients without CPM who were ATI positive [$p = 0.363$]. Median CRP value was 12.1 mg/ml [0.6–59.7] among the 9 patients with CPM and 2.4 [0–101] mg/ml among the 112 others [NS = non significant]. Six patients had elevated ANA.

In univariate analysis [Table 2], no factor associated with CPM could be identified, including age, gender, smoking status, age at IBD diagnosis, type of IBD, IBD localisation, concomitant immunosuppression, IFX regimen, number of infusions, IFX efficacy, median ITL value, and ATI positivity.

3.3. Rheumatological paradoxical manifestations

Among the 121 patients included, 10 [8%] patients developed an RPM at inclusion. They were mainly female [$n = 7$] and all had CD. Median age at at inclusion was 27 years [range: 12–45] and half of them were active smokers.

All cases of RPM consisted of inflammatory arthralgias affecting peripheral joints and requiring analgesic drugs. Arthralgias were bilateral and symmetrical in 9/10 cases, with night-time pain predominating on peripheral joints: wrists [$n = 5$], interphalangeals [$n = 4$], shoulders [$n = 3$], ankles [$n = 4$], and knees [$n = 2$]. Both CPM and RPM were observed in two patients.

Concerning treatments given for RPM, all the patients had received analgesics previously: analgesics grade I in all and grade II in three patients. One subject required non-steroidal anti-inflammatory drugs [NSAIDs] and one other systemic steroids.

Concerning treatment given for IBD, one patient with RPM was receiving a thiopurine in combination with IFX. Median number of IFX infusions at inclusion of RPM was 25 [11–32] and seven

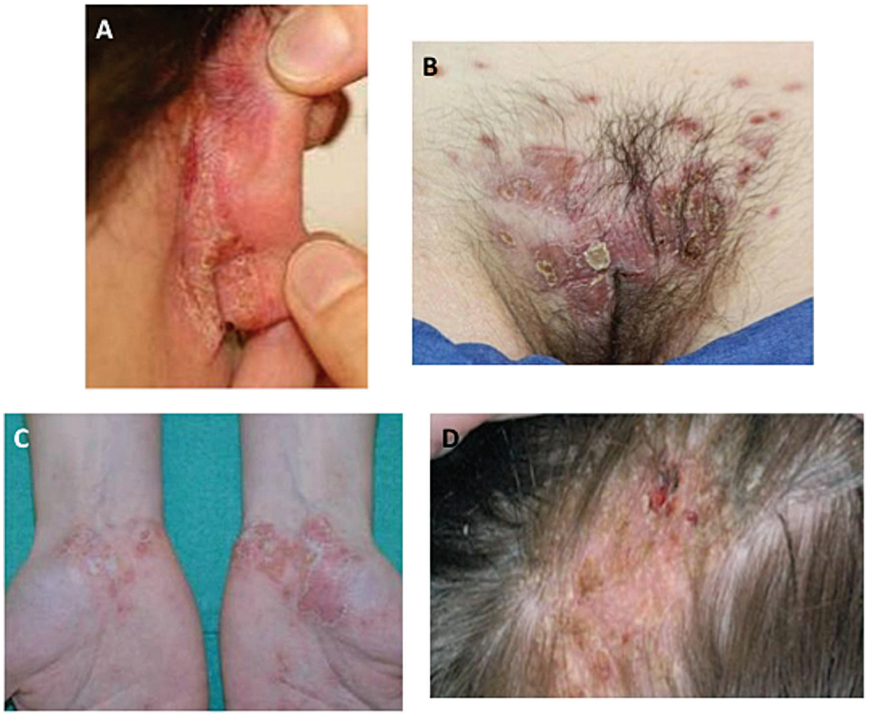

Figure 1. Typical features of cutaneous paradoxical manifestations related to infliximab. [A] Eczema with retro-auricular location. [B] Psoriasis with pelvic flexure location. [C] Psoriasis with palmar location. [D] Psoriasis lesions of the scalp.

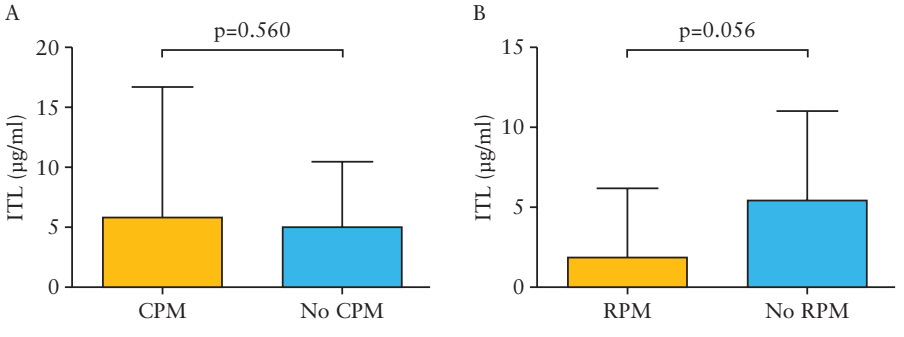

Figure 2. Median values of infliximab trough levels in patients with and without cutaneous paradoxical manifestations [A], and in patients with and without rheumatological paradoxical manifestations [B].

patients received more than 15 infusions. All patients were responding to IFX as maintenance, including seven in clinical remission.

In the 10 patients with RPM, median ITL value was 1.90 µg/ml [0.00–13.50] as compared with 5.57 µg/ml [0.00–49.12] among the 111 without RPM [p = 0.058] [Figure 2]. Three patients with RPM had positive ATI levels compared with 13/111 of the remaining patients [p = 0.127]. Median CRP value was 13.2 mg/ml [2.7–21.0] among the 10 patients with RPM and 1.9 [0–101] mg/ml in the 111 patients without RPM [NS]. Nine patients with RPM had ANA-positive levels [higher than 1/100], ranging from 500 to 8000 and including one patient with elevated anti-DNA antibodies and another one with detectable anti-histone antibodies.

In univariate analysis [Table 3], two factors were associated with RPM occurrence: active smoking [p = 0.026] and elevated ANA [p = 0.041]. In multivariate analysis, only ANA level above 1/100 was an independent factor in RPM, with an odds ratio of 8.21 (95% confidence interval [CI]: 1.01–66.87].

4. Discussion

In the present study, prevalence of paradoxical manifestations related to IFX given as maintenance therapy for IBD was less than 10%. No association between ITL and occurrence of CPM or RPM could be identified.

Over the past decade, occurrence of paradoxical manifestations related to anti-TNF has emerged as a new side effect of these agents, because such symptoms may have been first considered as IBD extra-intestinal manifestations by physicians. First to be described the incidence of skin manifestations has been observed in 10–22.5%[20,30,31] treated with IFX or with other anti-TNF agents. Several risk factors for developing such CPM under anti-TNF have been identified: female gender and personal or familial history of psoriasis or eczema. However, the pathogenesis of these paradoxical manifestations remains poorly understood. It has been suggested that such skin lesions are related to an induced cytokine unbalance in cutaneous tissue. Plasmacytoid predendritic cells infiltrating the skin increase

Table 2. Factors associated with cutaneous paradoxical manifestations in patients receiving infliximab as maintenance in univariate analysis.

Factor	*p*-Value
Female gender	0.076
Age at inclusion ≤ 27.4 years	0.163
Active smoking	1
Crohn's disease & indeterminate colitis [vs ulcerative colitis]	0.685
Associated immunosuppressant	0.390
Infliximab 5 mg/kg/8 weeks [vs other regimens]	1
Number of previous infliximab infusions > 15	0.315
Clinical remission	0.507
Infliximab trough levels ≤ 5.18 µg/ml	0.743
Absence of ATI	0.605

ATI, antibody to infliximab.

Table 3. Factors associated with rheumatological paradoxical manifestations in patients receiving infliximab as maintenance in univariate analysis.

Factor	*p*-Value
Female gender	0.513
Age at inclusion ≤ 27.4 years	0.743
Active smoking	0.026
Crohn's disease & indeterminate colitis [vs ulcerative colitis]	0.115
Associated immunosuppressant	0.686
Infliximab 5 mg/kg/8w eeks [vs other regimens]	0.751
Number of previous infliximab infusions > 15	0.198
Clinical remission	0.711
Infliximab trough levels ≤ 5.18 µg/ml	0.323
Absence of ATI	0.128
ANA > 1/100	0.041

ATI, antibody to infliximab; ANA, antinuclear antibodies.

the production of interferon-alpha [IFN-alpha] under the influence of anti-TNF.[32] This IFN-alpha increase has also been described by Seneschal *et al*. who observed that TNF neutralisation involved an enhancement in the production of MxA protein, correlated to IFN-alpha and to T lymphocyte recruitment via chemokine receptor CXCR3.[33] In a murine model, TNF-alpha blockade improved skin inflammation, markedly enhanced the expression of the pro-inflammatory cytokines such as interleukin-17, and suppressed Treg lymphocytes.[34]

Less is known about new-onset polyarthralgia in patients receiving anti-TNF. In a preliminary report from the Leuven group, it has been described in 21 patients who developed severe joint pain under anti-TNF. Interestingly, most of them harboured positive ANA levels and some were anti-DNA positive. Results from the present series are in the same line. Thus RPM seems to be a complex autoimmune disorder related to a lupus-like syndrome induced by TNFα blockade. Induction of ANA and anti-DNA antibodies by anti-TNF has been described over many years.[14,35] More recently, Beigel *et al*.[36] identified in their IBD cohort of 180 patients, 10% of patients having a lupus-like syndrome characterised by arthralgia, including two cases with severe symptoms requiring immediate anti-TNF therapy interruption. In multivariate analysis, anti-DNA antibodies values ≥ 9 U/ml was a predictive marker of developing this adverse event, whereas ANA levels ≥ 1/240 were not considered as an independent factor.

Pharmacokinetics of anti-TNF agents has become an important issue for managing patients with IBD. Indeed, patients with therapeutic anti-TNF trough levels have better disease outcomes and longer treatment duration. In daily practice, monitoring ITL can help the physician to optimise the treatment or to switch to another anti-TNF agent or to another biological with a different mode of action.[37] The impact of pharmacokinetics on anti-TNF side effects has been less explored. In a recent cohort study from Canada, median ITL was similar among the 9 patients with CPM and the 62 without [$p = 0.648$].[38] This finding has been confirmed in the present study, suggesting that anti-TNF pharmacokinetics is not involved in the occurrence of CPM. If so, one could speculate that decreasing the anti-TNF dosage cannot improve skin lesions related to the drug. IFX pharmacokinetics has been less studied on RPM. According to the present study, a relationship between ITL and such a paradoxical manifestation was nearly significant and cannot be excluded.

The present study has some limitations due to its limited sample size and its monocentric recruitment. Moreover, paradoxical manifestations have been first diagnosed by gastroenterologists on clinical symptoms. This suggests that CPM and RPM prevalence could have been underestimated, as only patients with the most severe manifestations have been recruited. Nevertheless, the prevalence of these manifestations is in accordance with previous reports from the literature. Importantly, this transversal cohort of IBD patients receiving maintenance with IFX who had been recruited consecutively is homogeneous and is one of the first looking for a potential association between IFX pharmacokinetics and the development of CPM and RPM. As in most previous studies, we have focused on trough levels. However, one could speculate that peak infliximab levels or area under the curve would be preferable.

In conclusion, disabling paradoxical manifestations related to IFX are observed in less than 10% of patients treated as with it as maintenance. Trough concentration of the drug does not seem involved in the development of CPM or RPM, which could be induced autoimmune disorders. Consequently, limiting the ITL by reducing the infusion dosage or increasing the interval between two infusions has probably no impact on these side effects. Better understanding of the pathogenesis of CPM and RPM may help to limit their development.

Funding

This work was supported by Theradiag [Marne la Vallée, France] providing kits for dosing infliximab trough levels and anti-infliximab antibodies [LISA-TRACKER® Premium Infliximab LTI001®, Biomedical Diagnostics BMD Society].

Conflict of Interest

FP: lecture fees from Abbvie and MSD. DL: consulting and lecture fees from AbbVie, Ferring, Janssen, MSD, Pfizer, and Takeda.

Acknowledgments

The authors thank Marie Beylot-Barry and Marie-Sylvie Doutre for their dermatological advice and Christophe Richez and Thierry Schaeverbeke for their rheumatological advice.

Author Contributions

CC, JC, DL: study conception and design, study investigations, data interpretation, statistical analysis, drafting and critical revision of the manuscript. FP, EC: study investigations, drafting and critical revision of the manuscript. MC:

statistical analysis and critical revision of the manuscript. PB: lab tests and investigator and critical revision of the manuscript.

References

1. Targan SR, Hanauer SB, van Deventer SJ, *et al.* A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;**337**:1029–35.
2. Hanauer SB, Feagan BG, Lichtenstein GR, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.
3. Rutgeerts P, Sandborn WJ, Feagan BG, *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;**353**:2462–76.
4. Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel J-F. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol* 2008;**6**:644–53.
5. Sands BE, Anderson FH, Bernstein CN, *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876–85.
6. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2008;**1**:CD006893.
7. Fidder H, Schnitzler F, Ferrante M, *et al.* Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009;**58**:501–8.
8. Caspersen S, Elkjaer M, Riis L, *et al.* Infliximab for inflammatory bowel disease in Denmark 1999–2005: clinical outcome and follow-up evaluation of malignancy and mortality. *Clin Gastroenterol Hepatol* 2008;**6**:1212–7.
9. Colombel J-F, Loftus EV, Tremaine WJ, *et al.* The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004;**126**:19–31.
10. Viget N, Vernier-Massouille G, Salmon-Ceron D, Yazdanpanah Y, Colombel J-F. Opportunistic infections in patients with inflammatory bowel disease: prevention and diagnosis. *Gut* 2008;**57**:549–58.
11. Deepak P, Sifuentes H, Sherid M, Stobaugh D, Sadozai Y, Ehrenpreis ED. T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha [TNF-α] inhibitors: results of the REFURBISH study. *Am J Gastroenterol*. 2013;**108**:99–105.
12. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology* 2012;**143**:390–9.
13. Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. *J Dermatol Treat* 2009;**20**:100–8.
14. Vermeire S, Noman M, Van Assche G, *et al.* Autoimmunity associated with anti-tumor necrosis factor alpha treatment in Crohn's disease: a prospective cohort study. *Gastroenterology* 2003;**125**:32–9.
15. Gottlieb AB, Evans R, Li S, *et al.* Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004;**51**:534–42.
16. Reich K, Nestle FO, Papp K, *et al.* Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005;**366**:1367–74.
17. Viguier M, Richette P, Bachelez H, Wendling D, Aubin F. [Paradoxical cutaneous manifestations during anti-TNF-alpha therapy]. *Ann Dermatol Vénéréologie* 2010;**137**:64–71.
18. Collamer AN, Guerrero KT, Henning JS, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: a literature review and potential mechanisms of action. *Arthritis Rheum*. 2008;**59**:996–1001.
19. Rahier J-F, Buche S, Peyrin-Biroulet L, *et al.* Severe skin lesions cause patients with inflammatory bowel disease to discontinue anti-tumor necrosis factor therapy. *Clin Gastroenterol Hepatol* 2010;**8**:1048–55.
20. Fréling E, Baumann C, Cuny JF, Bigard MA, Schmutz JL, Barbaud A, Peyrin-Biroulet L. Cumulative Incidence of, Risk Factors for, and Outcome of Dermatological Complications of Anti-TNF Therapy in Inflammatory Bowel Disease: A 14-Year Experience. *Am J Gastroenterol*. 2015 Aug;110(8):1186–96.
21. Van Moerkercke W, Ackaert C, Kasran A, Ballet V. Severe auto-immune driven arthralgia as a new side effect in anti-TNFα treated IBD patients? In: abstracts from the 5th ECCO Congress; February 2011; Dublin.
22. Subramanian S, Yajnik V, Sands BE, Cullen G, Korzenik JR. Characterization of patients with infliximab-induced lupus erythematosus and outcomes after retreatment with a second anti-TNF agent. *Inflamm Bowel Dis* 2011;**17**:99–104.
23. Allez M, Karmiris K, Louis E, *et al.* Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. *J Crohns Colitis* 2010;**4**:355–66.
24. Chowers Y, Sturm A, Sans M, *et al.* Report of the ECCO workshop on anti-TNF therapy failures in inflammatory bowel diseases: biological roles and effects of TNF and TNF antagonists. *J Crohns Colitis* 2010;**4**:367–76.
25. Van Assche G, Dignass A, Panes J, *et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohns Colitis* 2010;**4**:7–27.
26. Dignass A, Van Assche G, Lindsay JO, *et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. *J Crohns Colitis* 2010;**4**:28–62.
27. Satsangi J, Silverberg MS, Vermeire S, Colombel J-F. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.
28. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980;**1**:514.
29. D'Haens G, Sandborn WJ, Feagan BG, *et al.* A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007;**132**:763–86.
30. Cleynen I, Van Moerkercke W, Juergens M. Anti-TNF induced cutaneous lesions in IBD patients: characterization and search for predisposing factors. *Gut* 2010;**59**:A1.
31. Cleynen I, Vermeire S. Paradoxical inflammation induced by anti-TNF agents in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2012;**9**:496–503.
32. Nestle FO, Conrad C, Tun-Kyi A, *et al.* Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. *J Exp Med* 2005;**202**:135–43.
33. Seneschal J, Milpied B, Vergier B, Lepreux S, Schaeverbeke T, Taïeb A. Cytokine imbalance with increased production of interferon-alpha in psoriasiform eruptions associated with antitumour necrosis factor-alpha treatments. *Br J Dermatol*;**161**:1081–8.
34. Ma H-L, Napierata L, Stedman N, *et al.* Tumor necrosis factor alpha blockade exacerbates murine psoriasis-like disease by enhancing Th17 function and decreasing expansion of Treg cells. *Arthritis Rheum* 2010;**62**:430–40.
35. Nancey S, Blanvillain E, Parmentier B, *et al.* Infliximab treatment does not induce organ-specific or nonorgan-specific autoantibodies other than antinuclear and anti-double-stranded DNA autoantibodies in Crohn's disease. *Inflamm Bowel Dis* 2005;**11**:986–91.
36. Beigel F, Schnitzler F, Paul Laubender R, *et al.* Formation of antinuclear and double-strand DNA antibodies and frequency of lupus-like syndrome in anti-TNF-α antibody-treated patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2011;**17**:91–8.
37. Afif W, Loftus EV, Faubion WA, *et al.* Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010;**105**:1133–9.
38. Huang V, Dhami N, Fedorak D, *et al.* A study investigating the association of dermatological and infusion reactions to infliximab and infliximab trough levels. *Can J Gastroenterol Hepatol* 2015;**29**:35–40.