New onset of uveitis during infliximab treatment: A case report

Nouvelle apparition d'uvéite sous infliximab: À propos d'un cas

Mejda Bouladi[1,3], Amal Ben Othmen[1,3], Miladi Sawssen[2,3], Kalou Merieme[1,3], Ahmed Laater[2,3], Lamia El Fekih[1,3]

1. Ophthalmology Departmant. Mongi Slim University Hospital, La Marsa, Tunis, Tunisia.
2. Rhumatology Departmant. Mongi Slim University Hospital, La Marsa, Tunis, Tunisia.
3. Faculty of Medicine of Tunis, University of Tunis El Manar.

Abstract

Introduction: Anti-tumor necrosis factor α (anti-TNF α) agents are an effective treatment for a variety of inflammatory and autoimmune diseases. In ophthalmology anti-TNF α began to emerge as a possible therapy for non-infectious uveitis, paradoxically their administration may result in the onset or recurrence of inflammatory eye disease such as uveitis. We reported a case of new onset of bilateral anterior and intermediate uveitis in a patient with rheumatoid arthritis (RA) while being treated with infliximab and we performed a review of literature.

Observation: A 25-year-old female with RA under infliximab, presented with bilateral blurred vision. Anterior segment examination demonstrated retrodescmetic fine precipates, 1+ cells in the anterior chamber on both eyes. The fundus examination was difficult because of the vitritis. Fluorescein angiography demonstrated mild optic disc edema, and bilateral diffuse peripheral fern leaf cappilaritis. Optical coherence tomography showed severe cystoid macular edema bilaterally. The diagnosis of bilateral anterior and intermediate uveitis caused by infliximab was retained after exclusion of infectious and autoimmune aetiologies. She was treated with corticosteroid with good visual outcome.

Conclusion: In our case, new onset of uveitis may be considered as paradoxical effect of anti-TNF α therapy. Rheumatologists and ophthalmologists should be aware of this effect. Careful monitoring of patients under infliximab is necessary for appropriate diagnosis and early treatment.

Key words: case report, paradoxical effects, tumor necrosis factor-alpha.

Résumé

Introduction: Les anti-tumor necrosis factor α (anti-TNF α) représentent un traitement efficace dans plusieurs pathologies inflammatoires et auto-immunes. En ophtalmologie les anti-TNFα y compris l'infliximab commence à avoir une place dans le traitement des uvéites non infectieuses, paradoxalement leur administration peut être à l'origine d'inflammation oculaire. Nous rapportons le cas d'une nouvelle apparition d'uvéite antérieure et intermédiaire bilatérale chez une patiente suivie pour une polyarthrite rhumatoïde (PR) après l'introduction d'infliximab et nous proposons une revue de la littérature.

Observation: Une femme âgée de 25 ans atteinte de PR sous infliximab s'est présentée avec une diminution bilatérale de l'acuité visuelle. L'examen du segment antérieur au niveau des deux yeux a mis en évidence des précipités rétrodescemétiques fins, des cellules dans la chambre antérieure à 1+. L'examen du fond d'œil a été difficile à cause de l'hyalite. L'angiographie à la fluorescéine a mis en évidence un léger œdème papillaire et une capillarite diffuse bilatérale en feuilles de fougères. La tomographie par cohérence optique a montré un œdème maculaire cystoïde sévère en bilatéral. Le diagnostic d'uvéite bilatérale antérieure et intermédiaire causée par l'infliximab a été retenu après exclusion des étiologies infectieuses et auto-immunes. La patiente a été traitée par des corticoïdes avec amélioration de l'acuité visuelle.

Conclusion: Dans notre cas, la nouvelle apparition d'uvéite peut être considérée comme un effet paradoxal des anti-TNF α. Les rhumatologues et les ophtalmologistes doivent être conscients de cet effet. Une surveillance attentive des patients sous infliximab est nécessaire pour un diagnostic approprié et un traitement précoce.

Mots clés: à propos d'un cas, effets paradoxaux, tumor necrosis factor-alpha.

Correspondance
Mejda Bouladi
Ophthalmology Departmant. Mongi Slim University Hospital, La Marsa, Tunis, Tunisia.
Email: mejda.bouladi@fmt.utm.tn

Introduction

The recent introduction of biological agents has revolutionized the treatment of a variety of immune mediated-diseases such as chronic inflammatory rheumatic diseases (1). In particular, antitumor necrosis factor α (anti-TNF α) have shown efficacy in treating uveitis and reducing the incidence of flares (2). However, this new therapy was associated with unexpected side effects, such as relapse or new onset of uveitis in the absence of articular activity after initiation of treatment (1). These effects illustrate the possibility of a paradoxical effect of this type of therapy which are defined as the occurrence of a pathological condition that typically responds to a biological agent during therapy with this class of drug (3, 4). Wide range of ocular adverse events have been reported such as uveitis, scleritis, optic neuritis and more (1).

Paradoxical ocular inflammation in response to TNF inhibitors has been mainly observed with etanercept and in spondyloarthritis (3). Although less frequently, new onset of uveitis in patients with rheumatoid arthritis (RA) under infliximab has been also reported in the literature (3,4). The role of anti-TNF agents in the pathogenesis of ocular adverse events is still controversial (1).

We report here a rare case of new onset of bilateral anterior and intermediate uveitis in a patient with RA following administration of infliximab. Our literature review identified 26 other similar cases.

Observation

A 25-year-old female presented with sudden onset bilateral ocular redness and blurred vision.

She is known with seronegative and erosive RA since she was three years of age, the RA was initially managed with methotrexate for about fifteen years. Certolizumab one injection per month was added for about two years and was placed four months ago on Infliximab one injection per 8 weeks due to the disease's poor management. The last injection of infliximab has been received 1 week before symptomatology.

Upon examination, the best corrected visual acuity was 3/10 in both eyes. Intraocular pressure was normal. An examination of the anterior segment demonstrated retrodescmetic fine precipates, 1+ cells in the anterior chamber on both eyes. The fundus examination was difficult because of the vitritis. Fluorescein angiography demonstrated mild optic disc edema, and bilateral diffuse peripheral fern leaf capillaritis (Figure 1). Optical coherence tomography showed severe cystoid macular edema bilaterally (Figure 2).

A complete evaluation including tuberculin intradermal reaction, syphilis serology, angiotensin converting enzyme, HLA B 27 typing, chest X-ray had excluded infectious aetiologies, sarcoidosis and HLA-B27-associated uveitis. Behcet disease was eliminated due to the absence of bipolar aphthosis and a negative pathergic test. Cerebral magnetic resonance angiography was without abnormalities. The diagnosis of uveitis caused by Infliximab was retained.

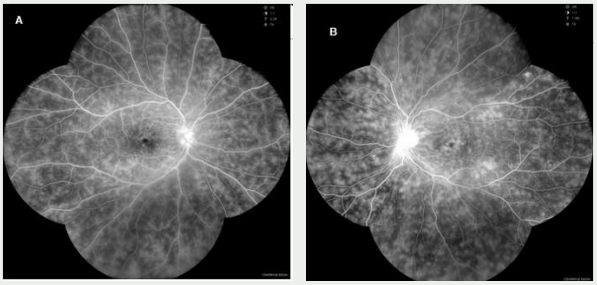

Figure1. Fluorescein angiography of the right (A) and left (B) eyes demonstrated mild optic disc edema, bilateral diffuse peripheral capillaritis and macular edema.

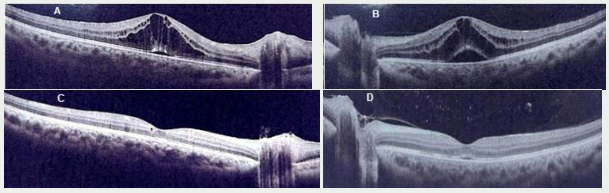

Figure 2. Macular optical coherence tomography findings:
(A and B) macular edema on both eyes at the first presentation
(C and D) disappearing of macular edema after three weeks of corticosteroids

Infliximab was not suspended and uveitis was treated with corticosteroid bolus for 3 days followed by transition to oral. Topical steroids have been also prescribed.

The patient's inflammation reduced significantly after 3 weeks of treatment. Fundus examination become accessible. Macular optical coherence tomography objectified a resolution of the cystoid macular edema (Figure 2).

Discussion

In our case, new onset of uveitis may be considered as paradoxical effect of anti-TNF α therapy. This uveitis may be interpreted in first analysis as an extra-articular disease feature, and not directly related to this therapy. Nevertheless, the RA was well controlled by anti-TNF α at time of occurrence of the uveitis and estimated prevalence of this event is low in RA under treatment on one hand. On the other hand, the atypical features for RA-related uveitis increase the likelihood that the uveitis is related to the therapy.

According to the literature, new onset of uveitis with anti-TNF-α for rheumatic conditions has been reported with a greater number of uveitis occurring with spondyloarthritis, less frequently with juvenile idiopathic arthritis and RA (3). It has been mainly observed with etanercept but infliximab and adalimumab can also induce ocular inflammation (3-5). Anterior uveitis was found in most cases, intermediate and posterior uveitis were reported less frequently (1).

Few cases of new onset uveitis with infliximab were reported in the literature. Lim et al. (6) reported 14 cases of new-onset uveitis with infliximab. Wendling et al. (3) reported five cases of new-onset anterior uveitis. Iwahashi et al. (7) reported four cases of new-onset

posterior uveitis with infliximab. Singla et al. (8) reported one case of bilateral anterior ocular inflammation in a patient with ulcerative colitis following administration of infliximab. Ben Abdelghani et al. (9) reported another case of new onset of bilateral retinal vascularitis occurring under infliximab in a patient with Crohn's related spondyloarthritis. Coates et al. (10) reported another case of new-onset bilateral uveitis in a patient with RA under infliximab. Pertinent data of different cases are illustrated in table 1. Clinical information was not available for the patients of Lim et al. (6).

Table 1. Cases of new onset uveitis during infliximab treatment in the literature

Authors/cases	Age (sex)	Disease	Uveitis type	Duration of expo (mo)	Modification infliximab	Outcome
Lim et al./14	No clinical information					
Coates et al./1	52 (F)	AS	_ / bilat	20	discontinued	uveitis resolved
Wendling et al./5	70(M)	AS	Ant/unilat	24	Continued	Retinal involvement
	40(F)	AS	Ant/bilat	38	Suspended 12 mo	Relapse after reintroduction
	47(M)	AS	Ant/unilat	35	Continued	Relapse after 1 yr
	51(M)	AS	Ant/unilat	11	Continued	Relapse after 6 yr
	64(M)	RA	Ant/unilat	10	Continued	Retinal involvement
Ben Abdelghani et al./1	41(M)	SPA+CD	vasculitis/bilat	24	Continued	No relapse after 20 mo
Singula et al./1	49(M)	UC	_/bilat	_	Continued	No relapse
Iwahashi et al./4	84(F)	RA	ME/unilat	4	Switch to TCZ	No relapse
	50(F)	RA	Vasculitis/unilat	5	Discontinued	No relapse
	14(F)	JIA	ME	10	Swith to ADA	No relapse
	17(M)	CD	Vasculitis+ME	24	Swith to ADA	No relapse

Expo: exposition, mo: months, F: female, M: mal, AS: ankylosing spondylitis, RA: rheumatoid arthritis, Ant: anterior, Unilat: unilateral, Bilat: bilateral, yr: years, SPA: spondyloarthritis, CD: Crohn's disease, UC: Ulcerative colitis, JIA: juvenile idiopathic arthritis, ME: macular oedema, TCZ: tocilizumab, ADA: adalimumab.

The exact mechanism behind this paradoxical effect is not completely understood but it's believed to be related to the complex role that TNF-α plays in the immune system and inflammatory processes (10). TNF-α has both pro-inflammatory and regulatory functions, and its disruption through anti-TNF α therapy might disturb the delicate balance of immune responses in some individuals, leading to unexpected outcomes such as uveitis (1,8,10).
The time range for the onset of uveitis varies between studies. In the study conducted by Iwahashi et al. (7), uveitis occurred 4 to 24 months after starting infliximab treatment. In this study, uveitis occurred two months following administration of infliximab.
This uveitis is time-limited without interrupting the TNF blocker in most of the case. Cessation of this drug and treatment with steroids are mandatory in same cases due to persisting or recurrence of uveitis (7,10).
Limitations of our study were difficulty of distinguishing uveitis related to underlying disease from paradoxical effect of anti-TNF α and the absence of prolonged follow up.
In conclusion, Rheumatologists and ophtalmologists should be aware of potential paradoxical effect when prescribing anti-TNF α agents, especially in patients with a history of uveitis or other autoimmune conditions. Careful monitoring and assessment of patients receiving these therapies can help to identify any adverse effects and tailor the treatment approach accordingly.

References

1. Nicolela Susanna F, Pavesio C. A review of ocular adverse events of biological anti-TNF drugs. J Ophthalmic Inflamm Infect 2020, 10(1).
2. Mahfoudhi M, Hariz A, Ben Abdelghani K, Turki S, Kheder A. Behcet's refractory uveitis treated successfully by infliximab. Tunis Med. 2014;92(1):41-2.
3. Cobo-Ibanez T, del Carmen Ordonez M, Munoz-Fernandez S, Madero-Prado R, Martin-Mola E. Do TNF-blockers reduce or induce uveitis? Rheumatology 2008, 47(5), 731–732.
4. Toussirot É, Aubin F. Paradoxical reactions under TNF-α blocking agents and other biological agents given for chronic immune-mediated diseases: an analytical and comprehensive overview. RMD Open 2016, 2(2), e000239.
5. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum 2007, 56(10), 3248–3252.
6. Iwahashi C, Ono H, Haruta M, Minami T, Mashimo H, Shimojo H, et al. New onset or exacerbation of uveitis with infliximab: paradoxical effects? BMJ Open Ophthalmology 2019;4:e000250.
7. Singla MB, Hodge DK, Moawad FJ. Infliximab-induced Anterior Uveitis in a Patient with Ulcerative Colitis. J Crohns Colitis 2015, 9(5), 432–432.
8. Ben Abdelghani K, Slouma M, Ben Jalel W, Zakraoui L. Retinal vasculitis: a novel paradoxical effect of anti-TNFα? BMJ Case Rep 2014. doi:10.1136/bcr-2014-204909.
9. Coates LC, McGonagle DG, Bennett AN, Emery P, Marzo-Ortega H. Uveitis and tumour necrosis factor blockade in ankylosing spondylitis. Ann Rheum Dis 2008, 67(5), 729–730.