original article

Cataract surgery under systemic infliximab therapy in patients with refractory uveitis associated with Behcet disease

Abullah Alfawaz,[a] Sultan Alrashidi,[b] Hatem Kalantan,[a] Hani Al-Mezaine,[a] Ahmed M. Abu El-Asrar*[a]

From the [a]Department of Ophthalmology, College of Medicine, King Abdulaziz University Hospital, Riyadh; [b]Department of Ophthalmology, Qassim University, Al Qassim, Saudi Arabia

Correpondence: Abdullah Alfawaz · Department of Ophthalmology, College of Medicine, King Abdulaziz University Hospital, PO Box 245, Riyadh 11411, Saudi Arabia · T: +966114775723 F: +966114775724 · abfz22@hotmail.com

Ann Saudi Med 2014; 34(4): 328-333

DOI: 10.5144/0256-4947.2014.328

*Dr. Nasser Al-Rashid Research Chair in Ophthalmology in his affiliation.

BACKGROUND AND OBJECTIVES: This study is to evaluate the outcome of cataract surgery in patients with refractory uveitis associated with Behçet disease (BD) treated with infliximab.

DESIGN AND SETTINGS: A retrospective study in a university-based tertiary referral center in the period between July 2003 and November 2011.

METHODS: This is a retrospective study of patients with refractory uveitis associated with BD who underwent phacoemulsification cataract surgery under systemic infliximab therapy between July 2003 and November 2011 at King Abdulaziz University Hospital, Riyadh, Saudi Arabia.

RESULTS: Six patients (9 eyes), 5 of which were male and 1 female, were identified in this study. The mean (SD) age and follow-up period were 26.2 (6.6) years (range, 16-36 years) and 51.6 (28.8) months (range, 12-84 months), respectively. All the patients underwent phacoemulsification with intraocular lens implantation. Postoperatively, visual acuity improved in all eyes and was 20/40 or better in 7 eyes (77.8%). In the immediate postoperative period, anterior chamber inflammation ranged from 2+ to 3+ cells. None of the patients developed inflammation relapse postoperatively. The most common postoperative complication was posterior capsular opacification in 5 eyes (55%), 4 of which were managed with neodymium:yttrium-aluminum garnet laser capsulotomy. Three eyes had glaucoma, 2 of which underwent successful glaucoma surgery and one was managed with topical antiglaucoma medications.

CONCLUSION: In patients with refractory uveitis associated with BD who are treated with infliximab, cataract surgery is safe and has a good prognosis.

Behçet disease (BD) is a chronic relapsing multisystem inflammatory disorder. Its diagnosis is based on criteria proposed by the International Study Group for BD in 1990.[1] Diagnosis requires recurrent oral ulceration and at least two of the following: genital ulceration, eye lesions, skin lesions, and a positive pathergy test. Ocular involvement, usually a bilateral nongranulomatous panuveitis running a chronic relapsing course, is present in about 70% of the patients and often causes marked visual impairment. Visual loss is typically caused by retinal vasculitis leading to occlusive vasculopathy. Therefore, recurrent BD uveitis must be regarded as a vision-threatening ocular inflammation and warrants an aggressive approach. The primary goals in managing patients with BD uveitis are rapid resolution of intraocular inflammation, prevention of recurrence, achievement of complete remission, and preservation of vision. Various nonspecific conventional immunosuppressive drugs, used alone or in combination, frequently fail to control inflammation or maintain remission.[2,3]

Several studies suggest a central pathogenetic role of tumor necrosis factor (TNF)-α, which, along with other proinflammatory cytokines, is produced by peripheral blood mononuclear cells as part of the inflammatory cascade.[4,5] Increased levels of TNF-α and soluble TNF receptors have been found along with other proinflammatory cytokines in the serum and plasma

of BD patients.[6,7] In addition, high levels of TNF-α have been found in the aqueous humor of patients with BD-associated uveitis.[8,9] The development of biologic agents, particularly those that target TNF-α, has heralded a new era in managing BD uveitis. Infliximab, a chimeric monoclonal antibody directed at TNF-α, binds with high affinity to the soluble and membrane-bound TNF-α, inhibiting a broad range of its biologic activities. Its long-term safety and efficacy in managing refractory panuveitis associated with BD[10-16] and its inducement of T cell development[17] have been shown.

At King Abdulaziz University Hospital, Riyadh, Saudi Arabia, BD-associated uveitis is the third most common cause for hospitalization among all uveitis patients.18 Cataract formation is a common complication in BD patients with an incidence ranging between 17% and 38.5%[3,19,20] and is reported to be as high as 77% in a large series of BD patients.[21] The pathogenesis of secondary cataracts in BD patients is multifactorial, as it is with other uveitic entities where recurrent inflammation, synechiae formation, and use of steroids are known risk factors.[22]

We report the outcomes of phacoemulsification cataract extraction and posterior chamber intraocular lens (PCIOL) implantation in patients with refractory uveitis associated with BD who failed to respond to conventional immunosuppresssive treatment and were treated with infliximab.

METHODS

After obtaining approval from the Institutional Review Board, the records of all patients with refractory vision-threatening uveitis associated with BD treated with infliximab between July 2003 and November 2011 at King Abdulaziz University Hospital, Riyadh, Saudi Arabia, were retrospectively reviewed. Nineteen patients (38 eyes) were identified, and in each, combination conventional immunosuppressive treatment failed to induce remission. Patients were managed and followed up by one of the authors (AMA).

The diagnosis of BD was based on the criteria defined by the International Study Group for BD.[1] Ophthalmic evaluation included best-corrected visual acuity on Snellen eye charts, measurement of intraocular pressure (IOP), biomicroscopic evaluation, and dilated indirect ophthalmoscopy. At presentation, all patients underwent corticosteroid therapy. In 4 patients, this began with intravenous methylprednisolone 1 g/d for 3 days followed by oral prednisone (1 mg/kg daily). Fifteen patients received oral prednisone only. The tapering of corticosteroid was according to the control of inflammation. Nonsteroid immunomodulatory therapy was used in all patients and included cyclosporine (5 mg/kg daily) in 16 patients (84%), azathioprine (2 mg/kg daily) in 2 patients (10.6%), and mycophenolate mofetil (2 g daily) in 1 patient (5.3%).

Intravenous infusions of infliximab, 5 mg/kg, were administered over 2 hours at weeks 0, 2, and 6, and then every 8 weeks. Adverse events were recorded throughout the study period. Ophthalmic evaluations were performed within 2 days of infusion, every 4 weeks, and whenever patients reported having symptoms. Each patient underwent a protein purified derivative skin test and chest radiograph as well as a general physical examination and laboratory evaluation before each infusion. This exam included a complete blood cell count, liver and kidney function test, antinuclear antibody test, and anti-double-stranded DNA antibody test.

Patients who had a significant cataract and completed at least 12 months of follow-up after phacoemulsification were included. Cataract surgery was indicated if it affected patient`s daily life or preventing complete if lens opacity affected patient`s daily life or prevented complete fundus exam. patients who had no ocular involvement and had cataract surgey before infliximab treatment, and patients with incomplete follow-up were excluded from the study. In all patients, ocular inflammation had been suppressed at least 3 months before surgery. In each instance, cataract surgery was timed to be performed within a week of infliximab infusion. Systemic medications were maintained. To dilate the pupil, phenylephrine (2.5%) and cyclopentolate (1%) were used every 15 minutes for 1 hour before surgery (3 doses each). Posterior synechias were released by synechiolysis with viscoelastic material or iris hooks. All patients underwent phacoemulsification with the implantation of PCIOL in the usual manner through a 2.8-mm corneal incision. At the end of the surgery, subconjunctival injection of 4 mg dexamethasone and 20 mg gentamicin was used. None of the eyes needed intracameral or intravitreal steroids. Postoperatively, topical prednisone acetate drops (1%) were used hourly for 3 days, every 3 hours for 1 week, 4 times daily for 1 week, and then tapered off. The frequency of topical steroid application was increased, and topical mydriatics were added when inflammatory reaction increased. Systemic medications were continued including regular infliximab infusions.

Statistical methods

Data were collected and stored in a spreadsheet using Microsoft Excel 2007.® Visual acuity was converted from Snellen value to the logarithm of the minimum angle of resolution (logMAR) for analysis. After data

cleaning, the analysis was carried out using SPSS version 19.0 (IBM Inc., Chicago, Illinois, USA). Descriptive statistics including means and standard deviations were calculated to describe continuous variables, while categorical variables were expressed as frequency and percent. The pre- and post-intervention means were compared using Wilcoxon signed-rank tests. Statistical significance was defined as $P<.05$.

RESULTS

The follow-up period after initiation of infliximab therapy ranged from 12 to 112 months with a mean (SD) of 44.1 (36.5) months, and the number of infliximab infusions ranged from 8 to 51 with a mean of 21.6 (14.6).

Cataract, as an ocular complication, was encountered during the follow-up period in 15 of the 38 eyes (39%). Of these, 9 eyes (6 patients; 5 males and 1 female) developed visually significant cataract and underwent phacoemulsification with PCIOL. The mean (SD) duration from presentation to cataract surgery was 29.8 (20.6) months (range, 8-72 months), while the age at surgery was 26.2 (6.6) years (range, 16-35 years). The mean number of infliximab infusions before cataract surgery was 14 (8.7) (range, 3-30) and the mean follow-up period of 29.4 (21) months (range, 6-84 months) before surgery.

Cataract extraction was performed without the significant exacerbation of the quiescent uveitis, and visual acuity was significantly improved from a preoperative mean logMAR of 1.19 (Snellen equivalent, 20/200) to 0.25 (Snellen equivalent, 20/40); $P=.008$ postoperatively; median (25% Quartiles) of 1.0 (0.7 – 1.6) to 0.1 (0.0 – 0.50) at a mean (SD) follow-up of 51.6 (28.8) months (range, 12-48 months) after surgery (see **Table 1**).

Seven of 9 eyes (77.8%) achieved visual acuity of 20/40 or better. The visual outcome was 20/200 in 1 eye because of optic nerve and retinal atrophy involving the macula after recurrent attacks of occlusive retinal vasculitis prior to presentation. None of the patients developed a postoperative fibrinous reaction in the

Table 1. Patient clinical characteristics.

Pt. No.	Preop VA	Day 1 VA	Last visit VA	Lens type	Complications	Interval between surgery and development of PCO (mo)
1 OD	20/60	20/30	20/20	Single piece (Lenstec Softec® IOL)	PCO managed by Nd:YAG laser capsulotomy	8
1 OS	20/200	20/40	20/20	Single piece (Lenstec Softec® IOL)	None	13
2 OS	CF 6ft	20/60	20/40	Single piece silicon IOL (STAAR Elastic Lens®)	PCO managed by Nd:YAG laser capsulotomy	8
3 OD	20/100	20/25	20/20	Single piece (Lenstec Softec® IOL)	PCO managed by Nd:YAG laser capsulotomy	14
3 OS	CF 2ft	20/60	20/28	Single piece (Lenstec Softec® IOL)	PCO managed by Nd:YAG laser capsulotomy	11
4 OS	CF 3ft	20/60	20/100	3-piece (Sensar® IOL)	Mild PCO	7 (Nd:YAG laser capsulotomy not needed)
5 OD	HM	CF 6ft	20/200	Single piece (AcrySof® IQ)	None	No PCO
6 OS	20/200	20/25	20/25	Single piece (AcrySof® IQ)	None	No PCO
6 OD	20/100	20/30	20/20	Single piece (AcrySof® IQ)	None	No PCO

VA: visual acuity; Preop: preoperative; Postop: postoperative; Phaco: phacoemulsification; OD: right eye; OS: left eye; CF: Counting fingers; HM: hand motion; PCO: posterior capsular opacity; Nd:YAG: neodymium:yttrium-aluminum garnet.

anterior chamber or pupillary membrane formation. Anterior chamber reactions ranged between 2+ and 3+ cells according to the standardization of Uveitis nomenclature.[23] Moreover, ocular tension was well controlled in all patients postoperatively. Three patients had concomitant glaucoma that was diagnosed prior to cataract surgery. Two needed glaucoma surgery after cataract extraction (trabeculectomy in one and deep sclerectomy in another), for the good control of IOP. One patient obtained the good control of IOP with TWO antiglaucoma medications. In the eyes that underwent glaucoma surgery, there was no exacerbation of uveitis. In addition, the filtering blebs were functioning during the follow-up period without the need for additional treatment.

No infections were observed after surgery. No patients developed macular edema as assessed by optical coherence tomography. The most common postoperative complication was posterior capsular opacifications in 5 eyes (55%), 4 of them managed by neodymium:yttrium-aluminum garnet (Nd:YAG) laser capsulotomy with the complete restoration of best-corrected visual acuity (**Table 1**). None of these developed complications after laser capsulotomy.

DISCUSSION

Cataract formation is a common cause of vision loss in patients with BD-associated uveitis. Safe and successful surgical intervention is essential for visual rehabilitation in these patients. Known causes of poor visual prognosis after cataract extraction in BD are severe posterior segment complications from recurrent retinal vasculitis, particularly an atrophy of the optic nerve and retina.[24-27] Therefore, a good control of inflammation with the use of anti-TNF-α therapy reduces these complications and consequently improves the results of surgical intervention.

Before the widespread use of infliximab therapy, cataract surgery in patients with BD-associated uveitis had a poor prognosis. Ciftci and Ozdemir[24] reported unsatisfactory visual outcomes in their patients because of posterior segment complications, particularly optic nerve atrophy. Süllü et al[25] reported the outcome of cataract extraction and intraocular lens implantation in patients with BD, finding that only 21% of the series achieved 20/40 or better visual acuity. We achieved this level of visual acuity in 77% of our patient population. The poor visual outcome in their series was because of preoperative optic atrophy and/or retinal atrophy involving the macula. Kadayifçilar et al[26] reported postoperative complications in 18 of 33 eyes that underwent cataract extraction [4 with fibrinous reaction, 2 with pupillary membrane formation, 2 with cystoid macular edema [CME], 6 with posterior synechiae, and 4 with severe posterior capsular opacity [PCO] that needed Nd:YAG laser capsulotomy]. None of our patients had fibrinous reaction, pupillary membrane formation, or CME. Five eyes in our series developed PCO, 4 of which underwent Nd:YAG laser capsulotomy with the complete restoration of the best-corrected visual acuity. As in another study of BD-associated uveitis patients who underwent cataract extraction, PCO was the most common postoperative complication that was found in 9 out of 19 eyes (47%).[25] In another study of BD patients who underwent phacoemulsification with PCIOL without the use of infliximab, only 16.7% achieved 20/40 or better visual acuity, and 52.8% developed PCO that was managed by neodymium:YAG laser capsulotomy.[27] Berker et al[28] reported the improvement of visual acuity to 20/40 or better in 18 of 40 eyes (45%) after cataract surgery. Our good outcome can be explained by the good control of inflammation in the pre- and postoperative periods.

To the best of our knowledge, the literature provides only 7 cases of BD where patients underwent cataract surgery under infliximab therapy.[29-31] Noda et al[29] first reported a patient with BD-associated uveitis unresponsive to conventional treatment who underwent cataract surgery in both eyes with an uneventful postoperative clinical course of infliximab therapy. Sakai et al[30] reported 3 cases of phacoemulsification in BD-associated uveitis, finding that intraocular surgery performed at the midpoint between infliximab doses improved the patient outcome. In another study of 5 patients with BD-associated uveitis who underwent intraocular surgeries, 3 underwent phacoemulsification. The authors found that infliximab had a potential benefit in reducing the complications of intraocular surgeries.[31]

After the complete control of uveitis was achieved with infliximab therapy, our group of 6 patients was able to undergo cataract surgery without a significant exacerbation of the quiescent uveitis. Infliximab appeared to make a significant contribution to improving uveitis management; concomitant immunosuppressive therapy was substantially reduced, and inflammation was well-controlled for at least 3 months before surgery. These factors contributed to favorable outcomes. In our series, 2 eyes underwent glaucoma surgery, IOP was controlled without antiglaucoma medication, and the filtering bleb was functioning during follow-up. Also, the preoperative use of systemic steroids was not needed, as infliximab maintained a good control of inflammation. Hence, we avoided the serious side effects

that may be caused by the use of high doses of systemic steroids.

One patient who, while receiving conventional treatment before presenting to our hospital, had recurrent inflammation and atrophy of the optic nerve and retina involving the macula, had a less favorable outcome. Infliximab therapy induced a good control of the inflammation, but damage to the retina and optic nerve was irreversible. The treatment course for this patient suggests that an early use of infliximab in patients with refractory uveitis assocated with BD is recommended to prevent irreversible damage. These findings in refractory uveitis associated with BD are consistent with previous studies and indicated that an early treatment of rheumatoid arthritis[32,33] and inflammatory bowel disease[34] with infliximab may improve the outcome and induce a permanent response that persists even after the discontinuation of the drug. Initial therapy with infliximab appears to alter the disease course. This could be the result of an early substantial reduction in the inflammatory process, after which minor treatment is sufficient to suppress and slow the disease process.[34]

We acknowledge the limitations of our small case series. Our results suggest that cataract surgery in patients with refractory uveitis associated with BD treated with infliximab is safe and has a favorable outcome. Adjuvant infliximab therapy leads to less pre- and postoperative ocular complications that improved the final outcome of cataract surgery in these patients.

Acknowledgments

The authors thank Ms. Connie B. Unisa-Marfil for the secretarial work. This work was supported by Dr. Nasser Al-Rasheed, Research Chair in Ophthalmology (Abu El-Asrar AM).

REFERENCES

1. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet. 1990;335(8697):1078-80.
2. Sakane T, Takeno M. New approaches to Behçet's disease. Expert Opin Investig Drugs. 2000;9:1993-2005.
3. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Huseyin Altunbas H, Urgancioglu M. Uveitis in Behçet's disease: an analysis of 880 patients. Am J Ophthalmol. 2004;138:373-80.
4. Mage JL, Dilsen N, Sanguedolce V, Gul A, Bongrand P, Roux H, et al. Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet's disease: a comparative study with familial Mediterranean fever and healthy subjects. J Rheumatol. 1993;20:1544-9.
5. Misumi M, Hagiwara E, Takeno M, Takeda Y, Inoue Y, Tsuji T, et al. Cytokine production profile in patients with Behçet's disease treated with infliximab. Cytokine. 2003;24:210-18.
6. Evereklioglu C, Er H, Turkoz Y, Cekmen M. Serum levels of TNF-alpha, sIL-2R, IL-6, and IL-8 are increased and associated with elevated lipid peroxidation in patients with Behçet's disease. Mediators Inflamm. 2002;11:87-93.
7. Bardak Y, Aridogan BC. The demonstration of serum interleukin 6-8, tumor necrosis factor-alpha, complement, and immunoglobulin levels in Behçet's disease with ocular involvement. Ocul Immunol Inflamm. 2004;12:53-8.
8. El-Asrar AM, Struyf S, Kangave D, Al-Obeidan SS, Opdenakker G, Geboes K, et al. Cytokine profiles in aqueous humor of patients with different clinical entities of endogenous uveitis. Clin Immunol. 2011;139:177-84.
9. El-Asrar AM, Al-Obeidan SS, Kangave D, Geboes K, Opdenakker G, Van Damme J, et al. CXC chemokine expression profiles in aqueous humor of patients with different clinical entities of endogenous uveitis. Immunobiology. 2011;216:1004-9.
10. Niccoli L, Nannini C, Benucci M, Chindamo D, Cassara E, Salvarani C, et al. Long-term efficacy of infliximab in refractory posterior uveitis of Behçet's disease: a 24-month follow-up study. Rheumatology (Oxford). 2007;46:1161-4.
11. Accorinti M, Pirraglia MP, Paroli MP, Priori R, Conti F, Pivetti-Pezzi P. Infliximab treatment for ocular and extraocular manifestations of Behçet's disease. Jpn J Ophthalmol. 2007;51:191-6.
12. Keino H, Okada AA, Watanabe T, Taki W. Decreased ocular inflammatory attacks and background retinal and disc vascular leakage in patients with Behçet's disease on infliximab therapy. Br J Ophthalmol. 2011;95:1245-50.
13. Tabbara KF, Al-Hemidan AI. Infliximab effects compared to conventional therapy in the management of retinal vasculitis in Behçet's disease. Am J Ophthalmol. 2008;146:845-50.e1.
14. Capella MJ, Foster CS. Long-term efficacy and safety of infliximab in the treatment of Behçet's disease. Ocul Immunol Inflamm. 2012 Jun;20(3):198-202.
15. Okada AA, Goto H, Ohno S, Mochizuki M; Ocular Behçet's Disease Research Group Of Japan. Multicenter study of infliximab for refractory uveoretinitis in Behçet's disease. Arch Ophthalmol. 2012;130:592-8.
16. Al Rashidi S, Al Fawaz A, Kangave D, Abu El-Asrar AM. Long-term clinical outcomes in patients with refractory uveitis associated with Behçet's disease treated with infliximab. Ocul Immunol Inflamm. 2013;21:468-74.
17. Sugita S, Yamada Y, Kaneko S, Horie S, Mochizuki M. Induction of regulatory T cells by infliximab in Behçet's disease. Invest Ophthalmol Vis Sci. 2011;52:476-84.
18. Al-Mezaine HS, Kangave D, Abu El-Asrar AM. Patterns of uveitis in patients admitted to a University Hospital in Riyadh, Saudi Arabia. Ocul Immunol Inflamm. 2010;18:424-31.
19. Pivetti Pezzi P, Gasparri V, De Liso P, Catarinelli G. Prognosis in Behçet's disease. Ann Ophthalmol. 1985;17(1):20-5.
20. Kazokoglu H, Saatci O, Cuhadaroglu H, Eldem B. Long term effects of cyclophosphamide and colchicine treatment in Behçet's disease. Ann Ophthalmol. 1991;23(4):148-51.
21. Yang P, Fang W, Meng Q, Ren Y, Xing L, Kijlstra A. Clinical features of chinese patients with Behçet's disease. Ophthalmology. 2008;115:312-318.e4.
22. Hooper PL, Rao NA, Smith RE. Cataract extraction in uveitis patients. Surv Ophthalmol. 1990;35:120-44.
23. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data: results of the First International Workshop. Am J Ophthalmol. 2005;140:509-16.
24. Ciftci OU, Ozdemir O. Cataract extraction in Behçet's disease. Acta Ophthalmol Scand. 1996;74:74-6.
25. Süllü Y, Oge I, Erkan D. The results of cataract extraction and intraocular lens implantation in patients with Behçet's disease. Acta Ophthalmol Scand. 2000;78:680-3.
26. Kadayifcilar S, Gedik S, Eldem B, Irkec M. Cataract surgery in patients with Behçet's disease. J Cataract Refract Surg. 2002;28:316-20.
27. Hu K, Lei B, Kijlstra A, Li P, Zhang X, Xiao X, et al. Male sex, erythema nodosum, and electroretinography as predictors of visual prognosis after cataract surgery in patients with Behçet disease. J Cataract Refract Surg. 2012;38:1382-8.
28. Berker N, Soykan E, Elgin U, Ozkan SS. Phacoemulsification cataract extraction and intraocular lens implantation in patients with Behçet's disease. Ophthalmic Surg Lasers Imaging. 2004;35(3):215-8.
29. Noda E, Yamanishi S, Shiraishi A, Ohashi Y. Cataract surgery under infliximab therapy in a patient with Behçet's disease. J Ocul Pharmacol Ther. 2009;25:467-70.
30. Sakai T, Kanetaka A, Noro T, Tsuneoka H. Intraocular surgery in patients receiving infliximab therapy for Behçet's disease. Jpn J Ophthalmol. 2010;54:360-1.
31. Nishida T, Shibuya E, Asukata Y, Nakamura S, Ishihara M, Hayashi K, et al. Clinical course before and after cataract and glaucoma surgery under systemic infliximab therapy in patients with Behçet's disease. Case Rep Ophthalmol. 2011;2:189-92.
32. Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to metrotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005;52:27-35.
33. van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ten Wolde S, Han KH, van Drugten MV, et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. Arthritis Rheum. 2007;56:2129-34.
34. Caviglia R, Ribolsi M, Rizzi M, Emerenziani S, Annunziata M, Cicala M. Maintenance of remission with infliximab in inflammatory bowel disease: efficacy and safety long-term follow-up. World J Gastroenterol. 2007;13:5238-44.