Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Infliximab and questionable efficacy of recommendations on tuberculosis screening

Introduction

Infliximab (Remicade®) is a TNF-alpha blocker, indicated for severe rheumatoid arthritis, Crohn's disease, psoriatic arthritis and ankylosing spondylitis. The European marketing authorisation was granted on 13 August 1999.
On 20 December 2000, the EMEA issued a warning on TBC infections during use of infliximab and recommended screening for latent and active TBC infections. Due to ongoing concerns for infections the EMEA, in a public statement dated 1 February 2002, limited the indications and recommended additional precautions against infections [1].

Concern: Despite these recommendations, the Netherlands Pharmacovigilance Centre Lareb still receives reports on TBC infections. This may question whether the health professionals take account of the recommendations and whether the recommendations for screening for TBC are effective. To answer these questions, the involved reports have been analysed.

Reports

Since 16 May 2001 until 29 June 2004 we received 15 reports (11 from MAHs, 4 from medical specialists) concerning 10 patients (9 with indication rheumatoid arthritis, one with Crohn's disease). Four reports concerned clinical trials by the MAH. See Table 1.
Two study reports (42428 and 44014) concern one patient. Due to the time between the first and the second TBC-events, the events have been reported separately.
Four patients died, four patients recovered, in one patient the infection is still ongoing, and for one patient no outcome was reported.
Two patients were reported as having disseminated tuberculosis.
In two patients information was available about the TBC-screening. One patient had a positive Tuberculin Purified Protein Derivative (PPD) skin test (13 mm) and a negative chest X-ray, and received prophylactic isoniazide. Infliximab was started together with isoniazide. At an unspecified moment, HIV antibodies were detected. The second patient had a positive PPD skin test and negative chest X-ray prior to study entry; she was treated with isoniazide for 6 months. Due to absence of isoniazide as concomitant medication, we assume that infliximab was started after cessation of isoniazide.
In the other 8 patients, including 2 study reports, no information was available on screening results.

Other sources of information

Literature

Several guidelines are available to distinguish absence of TBC-infection, latent (inactive), or active TBC-infection. All are based on medical history, PPD, chest X-ray, eventually in cooperation with a lung specialist, although cut-off points differ (Table 2).
In case of latent TBC-infection, prophylactic treatment (e.g. isoniazide for 6 to 9 months) is recommended. Whether this prophylactic treatment should be completed before infliximab can be started seems to be left to the treating physician, balancing the risk for tuberculosis against the risk for lack of control of rheumatoid arthritis. Horsburgh has extensively discussed the priorities of treatment of latent tuberculosis [2].
In case of active TBC-infection, all recommendations clearly state that treatment must be completed before treatment with infliximab can be started.

Table 2: Summary of treatment recommendations after screening

	latent	active
SPC [1]	Prophylactic therapy must be started before the initiation of Remicade, and in accordance with local recommendations. In this situation, the benefit/risk balance of Remicade should be very carefully considered.	If active tuberculosis is diagnosed, Remicade therapy must not be initiated (contraindication).
Guideline Dutch association of rheumatology [3]	Type of prophylactic therapy depends on previous anti TBC therapy No evidence available that initiation of anti TNF therapy during prophylactic therapy is safe. Due to HIV-experiences, anti TNF therapy might be started after at least 3 months of well-tolerated prophylactic therapy	Full course multidrug treatment of TBC. Preferably, postpone TNF blockade until completed. In serious cases of RA, consider starting TNF blockade during anti TBC therapy In case of multidrug resistant TBC, anti TNF treatment should be considered as contra-indicated
Arend SM. et al [4]	Strongly consider treatment. Delay TNF blockade.	Full course multidrug treatment of TBC. Postpone TNF blockade until completed.
Gardam MA. et al [5]	PPD-positive patient with a normal chest radiograph or a stable abnormal chest radiograph compatible with inactive tuberculosis plus negative sputum cultures should receive treatment for latent tuberculosis infection. Although a preferable approach is to wait until a full course of preventive therapy has been completed, if the clinical condition warrants it, anti-TNF therapy can be initiated 1-2 months after the start of prophylaxis if this therapy is well-tolerated.	Patients with active tuberculosis must be treated with a standard regimen and must have documented completion of therapy before anti-TNF therapy can be started

TNF: tumor necrosis factor; PPD: tuberculin Purified Protein Derivative skin test; TBC: tuberculosis; RA: rheumatoid arthritis

An emerging issue from literature is that TNF-alpha is required for an effective immune response, for granuloma formation, and to inhibit bacterial dissemination. TNF-alpha blockade may therefore result in extrapulmonary and disseminated tuberculosis infections, until now regarded as an atypical presentation [5]
Obrador reports 70 patients with TBC-infection in association with infliximab in Spain; in 56% extrapulmonary tuberculosis occurred, in 24% the infection was disseminated [6]. No information is available about tuberculosis screening results.

The Swedish Medical Product Agency reports 13 cases of tuberculosis in patients with TNF-alpha therapy. Ten patients are considered as reactivation of inactive tuberculosis, one as a primary infection, and two cases remain unclear. The MPA could not indicate whether screening recommendations had been followed; their results will be published [7].

Uthman *et al* reports about a patient with miliary TBC-infection despite negative PPD, negative chest X-ray and absence of exposure to active tuberculosis [8].

Armbrust *et al* report about a girl aged 9, with an extrapulmonary TBC-infection after infliximab, preceded by etanercept. Her PPD previous to etanercept was negative, possibly due to anergy [9].

Wolfe *et al* calculate that the incidence of tuberculosis is not raised by the diagnosis of rheumatoid arthritis, in contrast with treatment with infliximab. Their cases with TBC-infection during treatment with infliximab had no PPD in the two years before start of infliximab and did not receive prophylaxis. However, three had a positive PPD previously, and one was suspected for tuberculosis previously. Wolfe *et al* also estimate that 41% of their cases did not have a PPD before initiation of infliximab [10].

Keane *et al* analysed the FDA database with spontaneous reports from 1998 until May 2001 for tuberculosis during infliximab therapy. Seventy cases could be identified. Two cases noted possible recent exposure to tuberculosis, eight cases had a history of tuberculosis disease or infection. Twelve patients died. No information is available on screening results, possibly because they did not exist at that moment [11].

Wallis *et al* also analysed the FDA database with spontaneous reports from January 1998 until September 2002 for tuberculosis during infliximab therapy, and identified 335 cases. Due to the short latency time, they consider most TBC-infections as reactivations. This database stresses the limitations of PPD as a screening tool in patients with severe illness or immunosuppressive therapy [12].

Discussion

Despite recommendations, the Netherlands Pharmacovigilance Centre still receives reports on tuberculosis in association with infliximab. Together with literature data, this raises three concerns:

1. The SPC recommendation is insufficiently implemented by rheumatologists
2. Different recommendations exist, which may be confusing
3. The recommendation is insufficient to protect against TBC, and especially against TBC reactivation during or after prophylactic TBC therapy

References

1. EMEA. EPAR Remicade®. (version date 4-12-2003) http://www.emea.eu.int/humandocs/Humans/EPAR/Remicade/Remicade.htm.
2. Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. N.Engl.J Med 2004;350(20):2060-7.
3. J.W.G.Jacobs, M.A.F.J.van de Laar, A.E.Voskuyl, and H.E.Vonkeman. Richtlijnen overig: tuberculose en TNF-a-blokkerende therapie. Nederlands Tijdschrift voor Reumatologie 2004;
4. Arend SM, Breedveld FC, van Dissel JT. TNF-alpha blockade and tuberculosis: better look before you leap. Neth J Med 2003;61(4):111-9.
5. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, Vinh DC. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis 2003;3(3):148-55.
6. Obrador A, Lopez SR, Munoz P, Fortun J, Gassull MA. [Consensus guideline on tuberculosis and treatment of inflammatory bowel disease with infliximab. Spanish Working Group on Crohn Disease and Ulcerative Colitis]. Gastroenterol Hepatol 2003;26(1):29-33.
7. Boman G., Feltelius N., and Romanus V. Risk för tuberkulos vid behandling met TNF-alfa-hämmere. Flera fall i Sverige. (version date 2004) Information fran Läkemedelsverket 2004.
8. Uthman I, Kanj N, El Sayad J, Bizri AR. Miliary tuberculosis after infliximab therapy in Lebanon. Clin Rheumatol 2004;23(3):279-80.
9. Armbrust W, Kamphuis SS, Wolfs TW, Fiselier TJ, Nikkels PG, Kuis W, Wulffraat NM. Tuberculosis in a nine-year-old girl treated with infliximab for systemic juvenile idiopathic arthritis. Rheumatology (Oxford) 2004;43(4):527-9.
10. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004;50(2):372-9.
11. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345(15):1098-104.
12. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004;38(9):1261-5.

Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Table 1. summary of reports about tuberculosis in association with infliximab therapy

LRB	sender, source	report date, most recent date	M/F	indication	onset after first administration	co-immuno-suppression	co-medication	ADR	outcome	additional information on TBC
32003, 32686, 38698	specialist, MAH / literature, health professional	16-5-2001 2-7-2002	F 73	RA	14 weeks	MTX	captopril, bumetanide, triamterene, rabeprazol, folic acid, digoxin, prednisolon, isosorbidedinitrate, ferro fumarate, bisacodyl, glimepiride, paracetamol, midazolam	infection TBC, death	fatal	no history of TBC
34878	MAH / health professional	24-10-2001	F 60	RA	38 weeks			infection TBC	recovered with treatment	
37669	MAH / health professional	30-8-2002 15-10-2002	F 58	RA	3 months	prednison	risedronic acid	tuberculosis, pulmonary embolism, thrombophlebitis	unknown	
42570, 38337, 38516	MAH, specialist / **study**, health professional, literature	2-12-2002 27-11-2003	F 58	RA	76 weeks	MTX	INH, naproxen	respiratory insufficiency, infection TBC, pneumonia aspergillus, herpes simplex, liver functiuon tests abnormal	fatal	TST 13 mm, considered as latent TBC, INH and infliximab started 15-5-2001
40207	MAH / health professional	1-4-2003		RA				infection TBC, death	fatal	
40822	MAH / **study**	29-5-2003	M 40	RA	4.7 weeks	MTX, prednison	diclofenac, folic acid, temazepam, esomeprazol, alendronic acid,	Legionella pneumophilia infection, tuberculosis, uveitis, pneumothorax, ARDS	rehabilitation center	
42428	MAH / **study**	11-11-2003	F 67	RA	8,9 weeks	MTX	folic acid, levothyroxin, tramadol	disseminated tuberculosis	see LRB 44014	TST positive, chest X-ray negative, considered as latent TBC, INH for 6 months
42389	MAH / literature	14-11-2003	M 64	RA		prednison		pulmonary tuberculosis, death	fatal	
42900	specialist / health professional	29-1-2004 22-3-2004	F 52	Crohn	7 months	azathioprine	salazopyrin, venlafaxine	disseminated tuberculosis	recovered with quadrupple therapy	
44014	MAH / **study**	23-2-2004	F 67	RA	71 weeks	none	folic acid, pyridoxin, pyrazinamide, rifampycin, isoniazide, ethambutol, levothyroxin, irbesartan, tramadol	pyrexia, weight decreased, night sweats, pleural affusion	TBC diagnosed August 2003: 2 months after last administration; anti-TBC therapy started, now recurrent complaints and hospitalisation	**same patient as LRB 42428**
44928	specialist / health professional	29-6-2004	M 62	RA	20 weeks	azathioprine	naproxen, losartan-HCT, cervedilol	tuberculosis	recovered with triple therapy	