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THERAPY

The effectiveness for prevention of tuberculosis in patients with inflammatory rheumatic diseases treated with TNF inhibitors

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Abstract: *Background:* New biologic therapies blocking TNF undoubtly constitute a considerable advancement in the management mentioned diseases, but are also associated with higher risk of activation of tuberculosis. *Methods:* An assessment of tuberculosis activation rate in the group of patients with rheumatoid arthritis, juvenile idiopatic arthritis, ankylosing spondylitis and psoriatic arthritis threated by anti-TNF inhibitors since January 1st 2001 to June 30th 2007 in Slovakia and went in for special anti-tuberculosis screening before start of therapy.
Results: A total 537 rheumatic patients received the anti-TNF therapy. There were 346 rheumatoid arthritis patients, 68 juvenile idiopatic arthritis patients, 71 patients suffered from ankylosing spondylitis and 52 from psoriatic arthritis. Duration of anti-TNF therapy was 843 of patient-years. Infliximab took 203 patients with duration of therapy 348 patient-years, etanercept 201 patients with duration of therapy 331 patient-years and adalimumab 133 patients with duration of therapy 164 patient-years. The activation of tuberculosis reached the incidence 0.37 % (2 cases for 537 patients) representing 0.237 cases for 100 patient-years. Both patients had extrapulmonary forms of tuberculosis which was in one patient disseminated, but they fully recovered after the anti-TNF drugs were stopped and chemotherapy was completed.
Conclusion: Our results demonstrate a low incidence of tuberculosis activation during anti-TNF treatment in patients with inflammatory rheumatic diseases in the Slovak Republic and confirm the high effectiveness ours specified complex screening measures *(Tab. 3, Ref. 13)*. Full Text (Free, PDF) www.bmj.sk.
Key word: tumor necrosis factor, tuberculosis, infliximab, etanercept, adalimumab.

Despite the fact that the etiology of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis is still unknown, the study of pathogenesis revealed that these diseases share common mechanisms and are closely related. Tumor necrosis factor – alpha (TNF) plays an important role in the pathogenesis and the use of TNF inhibitors brings an advance in the treatment of patients with these inflammatory diseases, but is associated with the risk of tuberculosis (1) and malignancies (2). Activation of tuberculosis is a serious complication of anti-TNF therapy, because it is usually presented as extrapulmonary and disseminated form. This risk requires a safety screening for latent tuberculosis before the initiation of the therapy with TNF antagonists, as well as safety monitoring during a long-term application. The aim of our study was to evaluate the effectiveness of our screening for latent tuberculosis in the group of patients with inflammatory rheumatic diseases treated by TNF inhibitors.

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Methods

In the group of patients with inflammatory rheumatic diseases (rheumatoid arthritis – RA, juvenile idiopatic arthritis – JIA, ankylosing spondylitis – AS and psoriatic arthritis – PsA) a special screening has been performed for identification of latent tuberculosis. The screening was developed by rheumatologists in cooperation with pneumologists and consisted of the two main following items:

– Indications for anti-TNF therapy in all patients with inflammatory rheumatic diseases from Slovakia have been verified in the special diagnostic and therapeutic clinical centre in National Institute of Rheumatic Diseases in Piešťany. Healthcare personnel applying the therapy completed a special training aimed at determining the effectiveness and safety of anti-TNF treatment.

– Before initiation of the anti-TNF treatment and than once a year thereafter, each patient had to pass through an examination of personal history aimed at tuberculosis, a pulmonary physical examination, chest X-ray, and the intradermal tuberculin test (Mantoux II). Since July 1st 2006, all patients indicated for the anti-TNF therapy underwent the Quantiferon TB Gold Test. Therapy with anti-TNF blockers started only in patients without latent tuberculosis.

Results

A total of 537 rheumatic patients received the anti-TNF therapy (infliximab, etanercept, adalimumab) between 1st January 2001 and 30th June 2007 in the Slovak Republic. There were 368 women and 169 men aged between 18 and 78 years. Duration of the anti-TNF therapy was 843 patient-years. The number of patients treated with several anti-TNF drugs, their age and duration of treatment are presented in Table 1.

Since January 1st, 2001, 203 patients were treated with infliximab. The duration of therapy was 4178 patient-months, or 348 patient-years. Since April 1st 2003–201 patients were treated with etanercept, and duration of therapy was 3974 patient-months, or 331 patient-years. The therapy of adalimumab started on November 1st 2004 and since then 133 patients were treated with duration of therapy 1963 patient-months, or 164 patient-years. The indications for anti-TNF drugs in several inflammatory rheumatic diseases are shown in Table 2. Anti-TNF treatment has been indicated in 346 patients with RA, 68 patients with JIA, 71 patients with AS and 52 patients with PsA.

Among all our patients who have been monitored for serious adverse events, that caused the cessation of the anti-TNF therapy, we observed 2 cases of death (1 case following an acute gastrointestinal haemorrhage and 1 case following an unidentified malignant process, presumably abdominal, 4 months after anti-TNF treatment suspension; autopsy was not performed). The incidence of death was 0.237 cases for 100 patient-years (Tab. 3). Between January 1st 2001 and June 30th 2007, chronic latent TB has been activated in 2 patients – 0.37 % (2 cases/537 patients), representing an incidence: 0.237 cases for 100 patient-years. A specific peritonitis in 1 female, and a specific salpingo-ophoritis with subsequent dissemination in another female patient was observed. After that the anti-TNF treatment was stopped and the anti-tuberculosis combination therapy was initiated; an improvement in the overall condition and regression of clinical symptoms was observed. Thus the chronic latent tuberculosis, activated in the group of our patients during anti-TNF treatment, was extrapulmonary in one case and disseminated with an extrapulmonary onset in another case.

Discussion

Tumor necrosis factor (TNF) plays an important role in the pathogenesis of inflammatory rheumatic diseases, mainly the RA (3), and now is one of the targets of therapeutic inhibition. TNF antagonists currently available in Slovakia are: infliximab, a chimeric monoclonal antibody, etanercept, a soluble receptor binding protein and adalimumab, a fully human monoclonal antibody. At present, the effectiveness of anti-TNF treatment in RA is so important, that it allows us to consider the remission as the goal of therapy and not only the improvement of clinically symptoms. Until now, when the RA was treated by classical

Table 1.

n=537	TNF inhibitors		
	infliximab	etanercept	adalimumab
start of treatment	2001	2003	2004
number of patients	203	201	133
men	77	70	22
women	126	131	111
age (median)	48	39	50
treatment duration in months (median)	18	19	13
treatment duration in patient-monhts (median)	4178	3974	1963
treatment duration in patient-years (median)	348	331	164

Table 2.

n=537	TNF inhibitors		
	infliximab	etanercept	adalimumab
rheumatoid arthritis (346)	151	83	112
juvenile idiopathic arthrtiis (68)	5	62	1
ankylosing spondylitis (71)	32	34	5
psoriatic arthritis (52)	15	22	15

Table 3.

n=537 (1/1/2001-6/30/2007)	No of cases	%	No of cases for 100 patient-years
Chronic latent tbc activation	**2**	**0.37**	**0.237**
Pulmonary form of tbc	0	0	0
Extrapulmonary form of tbc	2	0.37	0.237
Death following tbc activation	0	0	0
Death during anti-TNF treatment	**2**	**0.37**	**0.237**
Hepatocellular carcinoma	1	0.19	0.119
Gastrointestinal haemorrhage	1	0.19	0.119

DMARDs, it was not possible to find out the remission rate. In patients with RA treated by anti-TNF antagonists (infliximab, etanercept, adalimumab) the prevalence of remission after 1 year of treatment ranges from 30 % to 49 % (4, 5, 6).

However the long-term safety of anti-TNF medications is not adequately known. TNF represents an important part of the human immune system response to infection. Its long-term therapeutic inhibition is associated with more frequent occurrence of common as well as opportune infections. Meta-analysis of clinical studies regarding infliximab and adalimumab suggests a higher risk of infectious complications and malignancies (2). Among the infectious complications, the reactivated tuberculosis (7) requires more attention, mainly due to extrapulmonary and disseminated form, which may have a fulminant course in immunosuppressed patients with inflammatory rheumatic diseases. The screening for chronic latent tuberculosis developed in Europe and North America can decrease the occurrence of tuberculosis activation during anti-TNF treatment (9). In our group of patients, we observed activation of tuberculosis in 2 among the total of 537 treated patients (0.37 %), with incidence of 0.237 cases for 100 patient-years. This value is comparable to tuberculosis activation observed during clinical studies with adalimumab (0.27 cases/ 100 patient-years) (10), but is lower compared to the data of Portuguese patients with inflammatory rheumatic diseases – 1.35 % (13 cases/960 patients) (11). In contrary to our results, the results of the Spanish register of patients with inflammatory rheumatic diseases treated with anti-TNF drugs (BIOBADASER) demonstrate even lower tuberculosis activation rate, which is the result of a more rigorous anti-tuberculosis screening. Since 2002, the tuberculosis screening before anti-TNF treatment in Spain has been tightened, and subsequently the incidence of tuberculosis decreased to 172 cases/100 000 patient-years (0.172 cases for 100 patient-years). Furthermore it was recognized that in cases, where the recommended screening wasn't fully accepted, the risk of tuberculosis activation increased 7 fold (12) and two-step tuberculosis skin test was the major failure in complying with recommendations. Data from Korean National Tuberculosis Association shown that risk of tuberculosis infection is 8.9-fold higher in Korean patient with RA and 30.1-fold higher in RA patients treated with infliximab, compared with the general Korean population (13).

Conclusions

Our results demonstrate a low incidence of tuberculosis activation during anti-TNF treatment in patients with inflammatory rheumatic diseases in the Slovak Republic and confirm the high effectiveness of our complex screening measures.

References

1. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD, and BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter aktive-surveillance report. Arthritis Rheum 2003; 48: 2122—2127.

2. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. J Amer Med Ass 2006; 295: 2275—2285.

3. Tetta C, Camuss, G, Modena V, Di Vittorio C, Baglioni C. Tumour necrosis factor in serum and synovial fluid of patients with active and severe rheumatoid arthritis. Ann Rheum Dis 1990; 49: 665—667.

4. Goekoop-Ruiterman YP et al. Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). Ann Rheum Dis 2007; 66: 1227—1232.

5. van der Neujde D et al. TEMPO Study Investigators. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006; 54: 1063—1074.

6. Breedveld FC et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006; 54: 6—37.

7. Núnez Martínez O, Ripoll Noiseux C, Carneros Martín JA, Gónzales Lara V, Gregorio Maraňón HG. Reactivation tuberculosis in a pacient with anti-TNF-alpha treatment. Amer J Gastroenterol 2001; 96: 1665—1666.

8. Stas P et al. Miliary tuberculosis following infliximab therapy for Crohn disease: A case report and review of the literature. Acta Gastroenterol Belg 2006; 69: 217—220.

9. Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. Nat Clin Pract Rheumatol 2006; 2: 602—610.

10. Schiff MH et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006; 65: 889—894.

11. Fonseca JE et al. and Grupo de Estudos de Artrite Reumatóide da Sociedade Portuguesa de Reumatologia. Tuberculosis in rheumatic patients treated with tumour necrosis factor sloha antagonists: the Portuguese experience. Acta Reumatol Port 2006; 31: 247—253.

12. Gómez-Reino JJ, Carmona L, Angel Descalzo M, and Biobadaser Group. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum 2007; 57: 756—761.

13. Seong SS et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis: effects of rheumatoid arthritis itself and tumor necrosis factor blockers. J Rheumatol 2007; 34: 706—711.

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