Letters to the Editor

Completion rate and compliance of anti-tuberculosis chemoprophylaxis in patients with rheumatic disease receiving tumour necrosis factor antagonists

Sirs,

Active tuberculosis (TB) is, in most instances, the result of reactivation of latent TB infection (LTBI) in patients with rheumatic disease (RD) receiving tumour necrosis factor (TNF) antagonists (1). Isoniazid (INH) treatment for 9 months is currently the preferred regimen as anti-TB chemoprophylaxis in persons with LTBI (2). In order to eliminate LTBI reactivation, improvements of treatment completion rate and compliance will be necessary.

A retrospective study of completion rate and compliance of anti-TB chemoprophylaxis was conducted using a questionnaire to patients. In addition, we collected various data by means of chart review and searches of the computer database. Between October 2003 and January 2008, patients receiving TNF antagonists were included in this study when prophylactic INH therapy was newly started. The duration and dosage of INH prophylaxis was decided by the treating physicians. Informed consent was obtained. Patients with LTBI who had received INH at least 6 months without interruption were classified as "completer". Medication compliance was defined as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen (3)". Patients with 100% compliance were classified as "compliant group", and others were "non compliant group".

Patients characteristics are shown in Table Ia. A total of 46 patients (96%) completed at least 6 months of INH. Two patients discontinued INH therapy due to hepatotoxicity, and could not receive INH therapy for 6 months. One patient experienced disturbance of vision in the fifth month, then INH was decreased from 300mg/day to 200mg/day. These adverse events diminished after cessation or reduction of INH. Reactivation of TB occurred in two patients in compliant group. Both of them safely recovered after anti-TB therapy.

As for compliance of INH therapy, forty-three patients (90%) answered 100% compliant with INH therapy (Compliant group). Compared with non-compliant patients (5 patients), compliant patients (43 patients) were (1) significantly older (mean age 57.9±10.3 yrs in compliant, *vs*. 45.4±15.4 yrs in non-compliant, p=0.019), (2) treated with etanercept (22 patients (51%), *vs*. no patients (0%), p=0.030), (3) with significantly more concomitant diseases (0.8±1.0, *vs*.0.2±0.4, p=0.036), (4) 100% compliant with other drugs (38 patients (88%) *vs*. 2 patients (40%), p=0.006) (Table Ib and c).

Table Ia. Characteristics of the 48 patients with rheumatic disease receiving INH and TNF antagonists.

Total patients number	48
Female	43 (90%)
Male	5 (10%)
Mean age ± SD (range)	56.6± 11.4 (25.8-72.9)
Disease	
Rheumatoid arthritis	46 (96%)
Undifferentiated arthritis	1 (2%)
Behçet's disease	1 (2%)
Duration of INH therapy	
9 months	42 (87%)
6 months	6 (13%)
INH completer	46 (96%)
Mean duration of INH therapy (mo)	8.4 ± 2.1 (2-12)
Dosage of INH	
300mg/day	39 (81%)
200mg/day	7 (15%)
100mg/day	2 (4%)
Adverse events	
Hepatotoxicity	2 (4%)
Disturbance of vision	1 (2%)
Compliance of INH therapy	96%
100%	43 (90%)
90%	1 (2%)
85%	1 (2%)
80%	1 (2%)
40%	1 (2%)
20%	1 (2%)

Multiple logistic regression analysis revealed that patients who were 100% compliant with other drugs were the only factor that was associated with 100% compliant with INH therapy when all effects were eligible for inclusion in the model.

The probability of developing active TB in patients receiving TNF antagonists was 7 times higher when recommendations were not followed (incidence rate ratio 7.09) (1). Anti-TB chemoprophylaxis with INH is most effective when the compliance rate is high (>80% of doses taken) (4). Previous studies have shown non-compliant rates varying between 8-33% (5). In this study, completion rate was 96% (46 of 48 patients) that was extremely higher than previous reports ranging from 27 to 76% (6). At the same time, treatment compliance was 96%. In a study with RA population (7), 60%-68% of the patients adhered to their disease modifying antirheumatic drugs and the rate of compliance were in agreement with previous studies.

In our study, 100% compliant with other drugs was the only independent factor associated with 100% compliant with INH by multiple logistic regression analysis. This tendency is reported in other classes of medications used to treat chronic conditions such as osteoporosis (8).

Patient's age and number of comorbidity contributed to INH compliance, even though these were not independent determinants in the multiple logistic regression analysis.

There was no association between education level, income, using excess alcohol, a

Table Ib. Comparison of characteristics between compliant group and non compliant group.

Variables	Compliant group (n=43)	Non compliant group (n=5)	p-value
Mean age ± SD (range)	57.9± 10.3 (25.8-72.9)	45.4 ± 15.4 (28.2-67.6)	0.019
Female	38 (88%)	5 (100%)	NS
Disease duration yrs ± SD (range)	6.7± 7.5 (0.4-40.9)	3.9 ± 3.5 (0.6-9.5)	NS
Type of TNF-α antagonists			
Infliximab	19 (44%)	4 (80%)	NS
Etanercept	22 (51%)	0	0.030
Both of infliximab and etanercept	2 (5%)	1 (20%)	NS
Adverse events of INH	2 (5%)	1 (20%)	NS
No. of comorbidity	0.8 ± 1.0 (0-4)	0.2 ± 0.4 (0-1)	0.036
Activity of RA (DAS28/CRP)			
Start of INH	5.1 ± 1.3 (3.1-7.5)	4.4 ± 0.5 (3.8-5.0)	NS
End of INH	2.8 ± 1.4 (1.0-6.3)	1.6 ± 0.5 (1.1-2.2)	NS
Difference between start and end	-2.2 ± 1.6 (-5.8-0.3)	-2.8 ± 0.2 (-3.2--2.6)	NS

Table Ic. Comparison of medication other than INH between compliant group and non compliant group.

Variables	Compliant group (n=43)	Non compliant group (n=5)	p-value
No. of previous DMARDs	3.1 ± 1.5 (1-7)	2.6± 1.5 (1-5)	NS
No. of concomitant drugs	6.0 ± 2.2 (1-12)	4.6± 2.1 (3-8)	NS
Methotrexate	33 (79%)	5 (100%)	NS
Dosage (mg)	6.7 ± 4.0 (0-14)	8.8± 2.3 (6-12)	NS
Prednisolone	27 (64%)	2 (40%)	NS
Dosage (mg)	3.4 ± 3.3 (0-15)	1.4± 2.2 (0-5)	NS
NSAIDs			
On consecutive days	25 (60%)	3 (60%)	NS
Per request medication	17 (40%)	2 (40%)	NS
Vitamin B6	32 (76%)	4 (80%)	NS
Dosage (mg)	14.3 ± 18.0 (0-60)	8.0± 4.5 (0-10)	NS
100% compliant with other drugs	38 (88%)	2 (40%)	0.006

lack of patient understanding of the benefits of therapy and completion rate or compliance (data not shown).

In addition to the retrospective study and small patients group, limitation of our study is based on patient self-report. However, contrary to popular belief, patient self-report is more reliable than doctor or nurse assessment of noncompliance (9).

Completion rate and compliance of INH was unexpectedly good in these patients. However, patients treated with TNF antagonists who are non-compliant with other drugs may require additional case management to improve compliance of anti-TB chemoprophylaxis.

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References

1. GOMEZ-REINO JJ, CARMONA L, ANGEL DESCALZO M: Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum* 2007; 57: 756-61.
2. Targeted tuberculin testing and treatment of latent tuberculosis infection: This official statement of the American Thoracic Society was adopted by the ATS board of directors, July 1999. This is a joint statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. *Am J Respir Crit Care Med* 2000; 161: S221-47.
3. CRAMER JA, ROY A, BURRELL A *et al*.: Medication compliance and persistence: Terminology and definitions. *Value Health* 2008; 11: 44-7.
4. SPYRIDIS NP, SPYRIDIS PG, GELESME A *et al*.: The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: Results of an 11-year randomized study. *Clin Infect Dis* 2007; 45: 715-22.
5. SZAKACS TA, WILSON D, CAMERON DW *et al*.: Adherence with isoniazid for prevention of tuberculosis among hiv-infected adults in South Africa. *BMC Infect Dis* 2006; 6: 97.
6. KWARA A, HEROLD JS, MACHAN JT, CARTER EJ: Factors associated with failure to complete isoniazid treatment for latent tuberculosis infection in Rhode Island. *Chest* 2008; 133: 862-8.
7. VAN DEN BEMT BJ, VAN DEN HOOGEN FH, BENRAAD B, HEKSTER YA, VAN RIEL PL, VAN LANKVELD W: Adherence rates and associations with nonadherence in patients with rheumatoid arthritis using disease modifying antirheumatic drugs. *J Rheumatol* 2009; 36: 2164-70.
8. CURTIS JR, XI J, WESTFALL AO *et al*.: Improving the prediction of medication compliance: The example of bisphosphonates for osteoporosis. *Med Care* 2009; 47: 334-41.
9. MACINTYRE CR, GOEBEL K, BROWN GV: Patient knows best: Blinded assessment of nonadherence with antituberculous therapy by physicians, nurses, and patients compared with urine drug levels. *Prev Med* 2005; 40: 41-5.