Cost-effectiveness analysis of strategies using new immunological diagnostic tests of latent tuberculosis infection before TNF-blockers therapy

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Summary

Several tests have been proposed to detect latent tuberculosis (LTB).

Objective > To evaluate the cost-effectiveness of different interferon-gamma release assays based strategies used to screen LTB before tumour necrosis factor (TNF) blockers initiation.

Methods > Consecutive patients with rheumatoid arthritis, spondyloarthritis or Crohn’s disease for whom TNF-blockers were considered, were recruited in 15 tertiary care centres. All were screened for LTB with tuberculin skin test (TST), Quantiferon TB Gold® in tube (QFT) and T-SPOT.TB® (TSpot) on the same day. Cost-minimization and cost-effectiveness analysis, testing 8 screening test combinations, were conducted. Effectiveness was defined as the percentage of LTB treatment avoided and compared with TST alone. Cost were elicited in the payer perspective, included all the costs related to the screening procedure.

These 2 authors have performed a similar amount of work and have to be considered a co-first author.
Introduction

The prognosis of patients with immune-mediated inflammatory diseases (IMID) such as rheumatoid arthritis (RA), spondyloarthopathies (SpA), Crohn’s disease (CD), psoriasis and juvenile idiopathic arthritis, has been transformed by the launch of TNF-blockers 15 years ago [1]. These treatments have been associated with an increased risk of either de novo tuberculosis (TB) or reactivation of latent tuberculosis (LTB) [2–4]. In RA, the excess risk of TB due to TNF-blocker treatment has been estimated to approximately 4 compared to RA controls not treated with such agents [5]. Thus, LTB screening has been considered essential prior to initiate any TNF-blocker and has been included in all national or international clinical practice guidelines [6,7].

Diagnosis of LTB relies on immunodiagnostic methods, which includes Tuberculin Skin Test (TST) and Interferon-gamma release assays (IGRAs). Developed more recently [8], IGRAs play a critical role in the field of LTB diagnosis. IGRAs test the capacity of circulating lymphocytes to release interferon-gamma in response to Mycobacterium Tuberculosis-specific antigens. The advantage of these tests relies on their capacity to detect an immune response specific to Mycobacterium Tuberculosis, with no cross-reaction with Bacillus Calmette-Guerin (BCG) vaccine or the majority of other non-tuberculosis mycobacteria. IGRAs seem to display a good sensitivity and a better specificity than TST [9]. Indeterminate results occur in 2.8%–6.4% [10] which constitutes an obvious limitation and their price, higher

Results > No tuberculosis reactivation was observed after TNF-blocker initiation. TST followed by QFT if TST was positive was found as the best screening strategy, i.e. the less costly (−54 € compared to reference) and most effective (effectiveness 0.93), resulting in an incremental cost-effectiveness ratio of −192 € per treatment avoided. A probabilistic sensitivity analysis confirmed this result in 72.3% of simulations.

Conclusion > TST followed by QFT if TST was positive is the most cost-effective strategy in screening for LTB in patients before starting anti-TNF therapy.

Résumé

Analyse coût-efficacité des stratégies utilisant les nouveaux tests diagnostiques immunologiques dans le dépistage de la tuberculose latente avant traitement par anti-TNF

De nombreux tests existent dans le dépistage de la tuberculose latente (TBL).

Objectif > Évaluer l'efficacité des stratégies basées sur les nouveaux tests à l'interféron (IGRAs) dans le dépistage de la TBL avant initiation d'un traitement par anti-TNF.

Méthode > Des patients consécutifs ayant une polyarthrite rhumatoïde, une spondylarthrite ou une maladie de Crohn chez qui un traitement par anti-TNF était considéré, ont été recrutés dans 15 centres. Tous les patients ont été dépistés pour la TBL par intradermoréaction à la tuberculine (IDR), Quantiferon TB Gold® in tube (QFT) and T-SPOT.TB® (Tspot) le même jour. Des analyses de coût-efficacité et de minimisation de coût, testant 8 combinaisons de tests de dépistage pour TBL ont été conduites. L’efficacité était définie comme le pourcentage de traitement pour TBL évité et comparé à l’IDR seule. Les coûts utilisés, dans la perspective du payeur, incluaient l’ensemble des coûts liés à la procédure de dépistage.

Résultats > Aucune tuberculose maladie par réactivation n’a été observée après initiation du traitement par anti-TNF. L’IDR suivie de QFT si l’IDR était positive était la meilleure stratégie de dépistage, c’est-à-dire, la moins chère (−54 € comparée à la référence) et la plus efficace (efficacité 0,93), se traduisant par un ratio différentiel coût-résultat de −192 € par traitement évité. Une analyse de sensibilité a confirmé ce résultat dans 72,3 % des simulations.

Conclusion > L’IDR suivie de QFT si l’IDR est positive est la stratégie la plus efficiente dans le diagnostic de la TBL avant initiation d’un traitement par anti-TNF.

TrialRegNo > NCT00811343.
than TST, remains a substantial concern in developing countries. In developed countries, the use of IGRAs is increasingly recommended [11,12]. In France, guidelines from the Health Authority [13,14] recommend IGRA in case of previous BCG, i.e. in the majority of the population.

To progress in IGRA evaluation, a study was conducted in France from 2008-2012 to assess the performance of the 3 different tests in the context of LTBI screening before TNF-blocker initiation as well as to identify the optimal test combination to minimize the risks of LTBI reactivation in the one hand and of unnecessary TB prophylaxis in the other hand. In this study, replacing TST with IGRA for determining LTBI infection allowed the proportion of patients with IMID needing prophylactic anti-TB antibiotics before beginning anti-TNF agents to be reduced by half [10]. We prolonged the previous clinical work by a cost-effectiveness assessment in order to identify the optimal LTBI screening procedure from a payer perspective and thus, to improve the strength of future guidelines.

Methods

Population sample

Patients with RA, SpA or CD with an indication for initial biologic treatment with TNF-blockers agents in 15 tertiary care hospitals were included in the ETAT study (TrialRegNo.: NCT00811343) [10]. Patients gave their informed consent to participate in the study and were followed for 1 year.

Strategies

Before TNF-blocker therapy was started, patients underwent TST and a blood sample was taken for QFT-Gold IT® (QFT) (Cellestis Limited, Chadstone, Vic., Australia) and T-SPOT.TB® (TSpot) (Oxford Immunotec, Abingdon, UK) within 3 days. The TST was carried out according to the intradermal Mantoux method with 0.1 mL of tuberculin purified derivative (Tubertest, Sanofi Pasteur, France). IGRAs were performed in 15 hospital laboratories (see acknowledgments) and interpreted according to the manufacturers’ instructions by local immunologists who were blind to the TST results [10].

Medico economic assessment

The economic analysis was performed from a payer perspective, i.e. the national health insurance perspective.

Costs

The study considered only the direct medical outpatient consultations, costs of tests, LTBI chemoprophylaxis (isoniazid plus rifampicin for 3 months) and its biological monitoring according to the national guidelines [7]. Consultation fees were obtained from the national tariff list (nomenclature générale des actes de biologie médicale (NABM)) [15]. As QFT and TSpot were not registered in NABM, their costs were obtained from the Nomenclature de Montpellier, dedicated to work-ups for which non-reimbursement tariff is available [16]. Indirect costs were not considered since the health payer perspective was chosen.

Effectiveness measure

De novo TB or LTBI reactivation prevalence after TNF-blocker initiation was considered as clinical outcome. As no tuberculosis reactivation was observed after TNF-blocker initiation [10], we conducted a cost-effectiveness analysis based on the number of LTBI treatment avoided, i.e. considered as the percentage of patient adequately untreated.

Model structure

A decision tree was used to represent the clinical pathways associated with diagnosis of LTBI before TNF-blocker. Eight different screening scenarios from several national recommendations were investigated:

- base strategy: TST alone which was considered as the reference strategy [6,7,11,13,14,17];
- strategy 1: TSpot followed by TST if TSpot was indeterminate [12,13];
- strategy 2: QFT followed by TST if QFT was indeterminate [12,13];
- strategy 3: TST followed by QFT if TST was positive [13,14];
- strategy 4: TST followed by TSpot if TST was positive [13,14];
- strategy 5: 2 IGRAs concomitantly, followed by TST if both IGRAs were indeterminate (Adapted from [12-14]);
- strategy 6: TSpot followed by QFT when TSpot was indeterminate, and TST if QFT was indeterminate (Adapted from [12-14]);
- strategy 7: QFT followed by TSpot when QFT was indeterminate, and TST if TSpot was indeterminate (Adapted from [12-14]).

Model parameters

Model was filled with probability values sourced from the ETAT study [10] and direct medical costs. The incremental cost (IC) was calculated by the difference between the strategy analysed and the base strategy TST. The incremental cost-effectiveness ratio (ICER) was defined by the difference in cost between two possible interventions, divided by the difference in their effectiveness. A probabilistic sensitivity analysis (PSA) based on Monte Carlo simulation of 1,000 repetitions/iterations explored the model uncertainty. Construction of the decision tree and all analyses were performed using TreeAge Pro 2012 (TreeAge Software Inc., Williamston, MA, USA).

Results

Patient characteristics

A total of 429 TNF-blocker naïve patients were included in ETAT study, of whom 392 (91.4%) had complete data, i.e. results for the TST and both IGRAs. Patient main characteristics were: males 162 (41.3%), median age 45 [IQR 34-56] and previous BCG immunization 257 (65.6%), RA 123 (31.4%), SpA 178 (45.4%) and CD 91 (23.2%). A total of 140 (35.7%) were treated...
by corticosteroids and 234 (59.7%) by immunomodulatory agents [10].

Costs
Costs of medical resource used in the study are presented in 2013 euro (Supplementary file 1). The strategy 3 – TST followed by QFT if positive TST – was the less costly with a total cost of 98 € and an incremental cost of –54 € (cost saving). Cost and incremental cost of the other screening strategies are shown in (Supplementary file 2).

Budget impact analysis
In 100 patients with rheumatoid arthritis, spondyloarthritis or Crohn’s disease for whom TNF-blockers are considered, the use of strategy 3 – TST followed by QFT if positive TST – compared to TST alone would save 5,400 € (= 100 × 54 €). In our cohort of 429 patients, the amount saved would have been 23,166 € (= 429 × 54 €).

Effectiveness
The most effective strategy, i.e. considered as the lowest percentage of patient adequately untreated compared with TST only (reference strategy), was also the strategy 3 (effectiveness: 0.93). Effectiveness of the other screening strategies are shown in (Supplementary file 2).

Incremental cost-effectiveness ratio
The ICER of strategy 3 was –192 € per inadequate treatment avoided and appeared to be the most cost-effective screening strategy. Decision tree including cost-minimization and cost-effectiveness analysis of the eight different screening scenarios, is shown in (Supplementary file 2). The PSA confirmed the results: the strategy 3 found to be the most cost-effective strategy in 72.3% of the simulations, followed by strategy 2 (26.2%), strategy 4 (1.4%) and strategy 1 (0.1%). A cost-effectiveness scatterplot is shown in (Supplementary file 3).

Discussion
In this Markov model, we examined the incremental cost-effectiveness ratio of seven different IGRA-based LTB screening strategies comparatively to TST in patients before starting TNF-blockers therapy. We have shown that replacing TST alone with TST followed by QFT if TST was positive in screening for LTB was the most cost-effective strategy. It allowed reducing the number of patients requiring antibiotic prophylaxis. Decreasing the number of LTB treatment leads to a diminution of cost but also to the small number of patients included. However, this lack of event was expected regarding the low annual incidence rate of TB for patients receiving anti-TNF therapy in the French population: 116.7 per 100,000 patient-years (95% CI 106.2–222.9 per 100,000 patient-years) [4]. Moreover, patients were followed during one year allowing a risk of late undiagnosed TB. Nevertheless, Tubach et al. demonstrated in the RATIO registry that the risk of TB was higher during the first year of anti-TNF treatment, thus limiting the risk of TB underestimation in our study [4].

Conclusion
From eight different IGRA-based LTB diagnostic strategies comparatively to TST in patients before starting TNF-blockers therapy, we have shown that replacing TST alone by TST followed by QFT if TST was positive is the most cost-effective strategy. These results could lead to a modification of guidelines for LTB screening procedure.

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Contributors: RF, BG, CF and BF had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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