Formulário de acesso a dados do Registo Nacional de Doentes Reumáticos (Reuma.pt) da SPR, 2012-2014

1. TÍTULO DO PROJECTO

Tuberculosis risk and prevention in Rheumatic Patients Treated with Biological Therapy

2. INTRODUÇÃO

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis* (MTB), associated with high morbidity, mortality and healthcare costs.[1]

Highly effective drugs inhibiting specific components of the pathways involved in several immune mediated inflammatory diseases (IMIDs), covering the fields of rheumatology, gastroenterology and dermatology, have been introduced in the clinical practice. These drugs, generally termed biologicals, target crucial players of the immune response, such as tumor necrosis factor (TNF), interleukin (IL)-1 beta, IL-6 or B-cells, have revolutionized the management of conditions such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA), inflammatory bowel disease and others.

An increased risk of active TB has been reported in IMIDs patients treated with TNF inhibitors in high incidence countries.[2-6] In RA this risk has been shown to be 1.6 to 25.2 times higher in patients treated with anti-TNF agents comparing to those taking only conventional immunosupressors.[3,7-11] In most cases, TB results from an activation of a previous latent infection (latent TB, LTB) a few months after the beginning of biological treatment,[12-15] namely TNF antagonists, and often presents an atypical course.[13,16]

TNF is a central effector in the defense against MTB, participating in formation and maintenance of granulomas. In fact, most of the evidence for new TB cases relates to anti-TNF drugs[3,7-11] and reactivation of LTB after administration of these agents has been demonstrated in animal models.[17]

With this background in mind, it is clear that preventive measures must be taken to avoid development of active TB in biological therapy users, particularly screening of LTB prior to treatment start. Guidelines have been developed by the Portuguese Society of Rheumatology (SPR) and the Portuguese Society of Pulmonology (SPP) since 2003[18,19,20,21]

Despite some experience in this field, available evidence on the best strategy to prevent the development of TB in biologic-treated patients is limited. At the moment, before starting anti-TNF agents (and other biologicals as well) Portuguese rheumatic patients are screened for LTB based on the clinical history, chest radiography (CXR) and tuberculin skin test (TST); more recently, interferon-γ release assay (IGRA) has also become available and has been included on the last national recommendations.[21]

Although this preemptive strategy is worthwhile and effective,[22] it is still far from perfect and even complying with all the screening guidelines some patients will develop active TB during treatment with biologicals.[2,3,23] On the other hand, the screening methodology is also selecting patients for LTB treatment on the basis of a very broad assessment strategy and concerns have been issued regarding the possibility of overtreatment, affecting the risk benefit ratio of LTB treatment in this group of patients. In Portugal, a survey on TB cases in rheumatic patients treated with anti-TNF drugs during the period of 1999-2005, i.e., prior to the introduction of national guidelines of TB prevention, has previously been published.[2] Thirteen cases were verified in 960 treated patients (1.35%), although 4 of these occurred before 2002 when no screening for LTB was performed.[2] To date, there haven't been other analyses of the TB incidence in biological users and the effectiveness of prevention measures has not been assessed. This is of crucial importance since Portugal has still, in the Western Europe context, a relatively high incidence of Tuberculosis. In fact, TB incidence was almost twice the incidence of Spain in the years 2000-2002, when the first major paper on this field was published, based exactly on the Spanish experience. Moreover, SPR has successfully implemented universal screening measures for LTB in a fast and effective fashion and the impact of this strategy, which differs slightly from that of other countries, including Spain, has not been objectively addressed.

We aim to study the hypothesis that TB incidence is increased in Portuguese rheumatic patients treated with biological therapy, compared to the baseline incidence of TB, since the introduction of these drugs. Furthermore we will test the hypothesis that TB incidence in such patients decreased after the introduction of specific screening measures for LTB applied at a global nationwide level.

The Rheumatic Diseases Portuguese Register, Reuma.pt, is a nationwide register of rheumatic patients treated with biologic and nonbiologic drugs available since June 2008,[24] capturing prospective data but also including available retrospective data collected in written

protocols. Reuma.pt has already been the source of several relevant publications on the use of biologics and constitutes the appropriate resource for assessing the impact of TB preventive measures.

3. OBJECTIVOS ESPECÍFICOS DO ESTUDO

1- Compare the incidence and characteristics of TB cases in rheumatic patients in two periods: before (1999-2005) and after (2008-2013) the introduction of specific guidelines for screening of LTB before the start of biologicals.
2- Analyze the effectiveness of TB prevention recommendations in rheumatic patients treated with biological drugs.
3- Determine the risk of TB in biological-treated patients in comparison with patients treated with conventional immunosupressors and with the general population.
4- Determine the safety of LTB treatment in biological-treated patients.

4. METODOLOGIA A APLICAR

We will conduct an incidence study, with a longitudinal retrospective cohort design. The primary outcome is the development of TB (pulmonary or extra-pulmonary forms). The independent variables will be the baseline rheumatic disease, epidemiological and clinical risk factors for TB – including place of birth, area of residence, travel to endemic areas, professional activity with increased risk of TB exposure, predisposing comorbidities (e.g., HIV infection, diabetes mellitus, primary immunodeficiency) – and exposure to corticosteroids, synthetic immunosuppressants and biological therapy.

Data on rheumatic patients with inflammatory joint diseases (RA, AS, PsA, JIA) treated with biological therapies will be retrieved from Reuma.pt. Missing data regarding TB screening and treatment will be inserted after consultation of the clinical record and/or contact with the rheumatology center. TB cases will be identified based on Reuma.pt data and confirmed with the National Program Against Tuberculosis (PNT) of the National Health Directorate (DGS) and with the Tuberculosis Committee (TC) of the SPP. Every Pulmonology Diagnosis Centre (CDP) will be contacted and asked for TB cases in rheumatic patients treated with biological therapy. Furthermore, a query will be sent to every center to confirm that there are no other non-reported TB cases in biologic-treated patients. Data from the period 1999-2005 will be confronted with the results reported in the article by Fonseca *et*

al relating to the same period.[2] The goal is to identify all TB cases in rheumatic patients since the introduction of biologics. This will also allow improvement of the quality of data in Reuma.pt and auditing the reasons for the missing information detected.

Furthermore, data on a similar number of age- and sex-matched patients of each disease group not exposed to biological therapies will also be acquired through the same process as described above.

To calculate the person-time of exposure to biologicals we will rely on data from Reuma.pt for treatments started after 2008. For treatments prior to 2008, we will retrospectively collect data by contacting the Rheumatology departments in question and use data collected for the preliminary analysis of patients on biologics in 2005.[25,26] Furthermore, we will ask for data from the hospital pharmacies nationwide as well as pharmaceutical companies and estimate the mean biological exposure (in person-years).

The incidence rate of TB in rheumatic biologic users (per 100,000 patient-years) will be calculated and divided into two periods: before (1999-2005) and after (2008-2013) the introduction of specific guidelines for TB prevention. These rates will be compared: between them, with those observed in patients who have not been treated with biologicals and with incidence rates reported for the general population. This will enable the determination of the real impact of such recommendations on development of new TB cases and the relative risk of biological therapy comparing to rheumatic patients treated with nonbiologics and to the general Portuguese population. Furthermore, we will be able to compare our results with those reported in other European countries, such as Spain,[3] France[27] or the United Kingdom.[10] We will also assess the percentage of patients assigned for LTB treatment and register serious adverse events related to the use of the drugs used for LTB treatment.

TB cases in rheumatic patients treated with biological therapy will be analyzed and thoroughly characterized in terms of disease and patient features, biological agent used, treatment duration before diagnosis and TB features (location, screening, diagnostic, treatment, outcome). Additionally, screening results and prophylaxis/treatment of LTB in rheumatic patients will be examined. Based on these results, screening procedures (CXR, TST, IGRA) will be studied on their global effectiveness in detecting LTB / avoiding active TB and inter-test concordance (TST-IGRA) will be determined (Kappa test).

5. LIMITAÇÕES E RESULTADOS EXPECTÁVEIS

With this study, we expect to detect a beneficial effect of the introduction of the national recommendations for the prevention of TB on the incidence rate of TB in patients treated with biological therapies, with a reduction in the number of cases seen in the period of 2008-2013 compared to 1999-2005. Furthermore, we expect to confirm that despite the prophylaxis measures, TB occurs more frequently in these patients than in the general population and than in the IMIDs patients treated with nonbiological drugs.

Regarding TB cases, and based on previous results,[2,4] it is predictable that the majority of the cases will occur after exposure to anti-TNF agents, particularly monoclonal antibodies (infliximab, adalimumab, golimumab). Additionally, we will see whether the incidence of TB will be raised in patients using other, non-anti-TNF biologicals. It is expectable that these drugs will not significantly increase the rate of TB infection, given their lower influence on defense pathways against MTB.

Analysis of the TB cases will allow us to study the effectiveness of screening tests such as TST and IGRA, better clarifying their role in LTB diagnostic and treatment. Finally, we will also assess the occurrence of serious adverse effects during LTB treatment in order to clarify the risk benefit ratio of this screening strategy. These results will either reinforce the screening and treatment strategy used so far or may highlight the need for adapting it.

Possible limitations of the study include difficulties in obtaining all the TB cases in biologic-treated rheumatic patients, although we expect to obviate this by a thorough screening and search strategy, in different, parallel channels. Another limitation, eventually harder to confront, is the calculation of the overall exposure to biologicals in person-years. This is related to both the treatment strategies, with sequential drug switch, and the fact that data on the first years when biologic therapy became available (1999 onwards) is probably less complete than later treatments. To face this issue, we will use data collected on patients with RA[25] and AS[26] treated with biologics from 1999 to 2005 that were thoroughly characterized and published, which will enable accurate data for patients in this period. For more recent treatments we will use biologic exposure data from ReumaPT, an approach used by others in the literature.[3,4]

6. CALENDARIZAÇÃO DAS TAREFAS

Data collection on TB cases and their respective characteristics will be performed from March through November 2014, together with the estimates for biologicals exposure in rheumatic patients. Data analysis will follow in the next 3 months, culminating with a publication in a national and international relevant journal in the field of Rheumatology.

7. EQUIPA DO TRABALHO

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8. FINANCIAMENTO E CONFLITO DE INTERESSES

None.

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