

(p-ANCA and c-ANCA, respectively) were negative. Serum C3 and C4 levels were decreased (30 mg/dL and 7 mg/dL, respectively). According to results, a diagnosis of SLE presenting with acute pneumonitis was made. On the 4th day, the patient was started with 1 g intravenous methyl prednisolone once a day for 3 days, followed by tablet hydroxychloroquine 400 mg daily and tablet prednisone 1 mg/kg daily for 6 weeks with gradually tapering of prednisolone to a maintenance dose of 10 mg daily. From two months after, her chest X-ray has shown practical resolution (Fig. 1C). At six months later, computed tomography described adhesions of the right side with no other specific abnormalities (Fig. 1D).

Acute lupus pneumonitis (ALP) is an uncommon manifestation of lupus, affecting less than 2% of cases. It is often life threatening once ventilator failure sets in, with mortality rate of more than 50%, despite of the treatment.<sup>3</sup> The main pathology in ALP could be the acute alveolar capillary unit injury.<sup>4</sup> Lupus pneumonitis presents with acute onset of fever, cough, tachypnea and hypoxia. The usual radiological sign of lupus pneumonitis is consolidation in one or more lung areas, typically basal and bilateral, often associated with pleural effusion and pulmonary arterial hypertension.<sup>5</sup> Our case was difficult to diagnose at first, since the onset symptoms indicated infection etiology and do the relevant work up. We have excluded infective pneumonia by repeated sputum analyses and single BAL fluid examination; alveolar hemorrhage since there were no hemoptysias and Hemosiderin-laden macrophage was absent in BAL fluid. The mainstay of acute lupus pneumonitis treatment is the systemic corticosteroids usage (prednisone 1–1.5 mg/kg/d divided accordingly), although despite high-dose corticosteroid usage, the lupus pneumonitis mortality remains high.<sup>3</sup> If there is no response to oral corticosteroids within 72 h and the patient has marked tachypnea, hypoxemia or suspected diffuse alveolar hemorrhage, treatment should include intravenous corticosteroid pulse therapy (i.e., 1 g methylprednisolone per day for 3 days).<sup>3</sup> The corticosteroid improvement was impressive in our case, noticed on the very first day.

In conclusion, acute lupus pneumonitis can be the initial manifestation of SLE. ALS diagnosis is essential, by excluding other causes of lung infiltration, such are infective pneumonia (bacterial, mycobacterial, fungal and viral), organizing pneumonia (OP), alveolar hemorrhage, pulmonary embolism and volume

overload state, due to either renal failure or to congestive heart failure.<sup>6</sup> Also, it is critically important to differentiate ALP from diffuse alveolar hemorrhage (DAH) which may have similar clinical presentation, laboratory immunology testing (ANA, anti-dsDNA) and radiographic findings, with almost equally grave prognosis. ESR and CRP may be used to support clinical suspicion. Unlike ESR, CRP (or hs-CRP) elevation is only modest in active SLE without infection, while a high hs-CRP level (>5–6 mg/dL) is a strong predictor of infection. Also, ESR/CRP ratio  $\geq 15$  suggests lupus flare, while ratio  $< 2$  suggests infection.<sup>7</sup>

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1579-2129/

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## Application for Authorization for Therapeutic Use of Beta-Adrenergic Agonists and Inhaled Corticosteroids in Athletes with Asthma<sup>☆</sup>



### La solicitud de autorización de uso terapéutico para agonistas betaadrenérgicos y corticoides inhalados en el deportista con asma

Dear Editor,

Since 1972, when Rick Demont lost his gold medal in Munich for using banned medication, anti-doping legislation in the field of asthma and sport has gradually become more fit-for-purpose, simplifying the lives of athletes with asthma, and consequently those of their doctors. Since January 2013, asthma can be treated without any significant restrictions, and the requirement to request permission from official sporting bodies has been lifted.<sup>1,2</sup> However, the

regulations must be read carefully, because authorizations for use are based on the administration of therapy as stipulated. Section S3 of the regulations reads as follows<sup>3</sup>: “All selective and non-selective beta-2 agonists and all their optical isomers are prohibited. These include, but are not limited to: fenoterol; formoterol; higenamine; indacaterol; olodaterol; reproterol; salbutamol; salmeterol; terbutaline; vilanterol. Exceptions: inhaled salbutamol: maximum 1,600 mcg over 24 h, without exceeding 800 mcg over 12 h; inhaled formoterol: maximum delivered dose 54 mcg over 24 h; inhaled salmeterol: maximum 200 mcg over 24 h. This corresponds to higher dose ranges than the therapeutic doses of the 3 products. The presence in urine of a concentration of salbutamol higher than 1000 nanograms per milliliter or formoterol higher than 40 nanograms per milliliter will be assumed to reflect use of the substance for non-therapeutic intentions and will be considered an adverse analytical finding (AAF), unless the athlete proves, in a controlled pharmacokinetic study, that this adverse finding was the consequence of the use a therapeutic dose (by inhalation) at the maximum dose indicated above”. That means, therapeutic doses of salbutamol, salmeterol and/or formoterol are permitted alone or in combination with any inhaled corticosteroids available on the pharmaceutical market. In these cases, no Therapeutic Use

<sup>☆</sup> Please cite this article as: Drobnic F, Blanco-Alfaro J. La solicitud de autorización de uso terapéutico para agonistas betaadrenérgicos y corticoides inhalados en el deportista con asma. *Arch Bronconeumol.* 2018;54:223–225.

**Table 1**  
Decisions on Therapeutic Use Exemption applications assessed by the Therapeutic Use Exemption Commission of the Spanish Agency for the Protection of Health in Sport in 2015.

Therapeutic Authorizations Processed in 2015 – n: 465					
Beta2 Agonists	Applications	Not Applicable	Rectification	Granted	Not Granted or Refused
Formoterol	23	23			
Salbutamol	31	31			
Salmeterol	7	7			
Terbutaline	69 (52.6%)		17 (24.6%)	39 (56.5%)	13 (18.8%)
Vilanterol	1			1 (100%)	
Total	131	61 (46.6%)	17 (13%)	40 (30.5%)	13 (9.9%)
Corticosteroids	Applications	Not Applicable	Rectification	Granted	Not Granted or Refused
Prednisone	36		2	31	5
Budesonide	27	24 (88.9%)	1	3	
Fluticasone	27	26 (96.3%)	1	1	
Methylprednisolone	25		1	23	2
Dexamethasone	23		2	21	2
Betamethasone	15	10 (66.7%)	2	4	1
Deflazacort	15			15	
Triamcinolone	9	6	2	3	
Beclomethasone	8	7 (87.5%)		1	
Mometasone	3	3 (100%)			
Ciclesonide	1	1 (100%)			
Methylprednisone	1			1	
Others	2				2
Total	192	77 (40.1%)	11 (5.7%)	103 (53.6%)	12 (6.3%)

The percentages of the most significant applications are shown. Those for betamethasone and budesonide are not limited to asthma and also apply to anti-inflammatory therapies for other systems. No applications for use in asthma were denied.

Exemption (TUE) is required, and the medical practitioner needs only to attend his/her patient. If one of the prohibited bronchodilators is considered essential due to the patient's characteristics or treatment history, or to improve adherence, wellbeing or ease of use, *etc.*, the reason for this decision must be explained, and a TUE application must be submitted to demonstrate that this subject is asthmatic and experiences real bronchial hyperresponsiveness. In the application, the following points must be addressed: (1) the patient's disease must be demonstrated on the basis of detailed reports and validated clinical tests<sup>4</sup>; (2) it must be made clear that the prohibited substance or method in question is necessary to treat an acute or chronic medical problem which, if untreated, would cause a significant deterioration in the individual's health; (3) that there is no reasonable therapeutic alternative to the use of the prohibited substance; and (4), that is highly unlikely that this treatment will improve the individual's performance more than that what could be achieved from restoring them to their normal state of health.<sup>5</sup> The reason for the prohibition of some beta-2-agonists is not a whim or a financial maneuver from pressure groups, but is based on point 4 of the TUE criteria listed above: these substances at therapeutic doses are useful for the treatment of asthma, but at high concentrations they also have performance-enhancing effects,<sup>6,7</sup> and can be used by some individuals for unethical purposes.

If, as doctors, we perform our work efficiently, this will impact the efficacy of everyone involved: not only the patient, but also the entire community, the family, the sporting bodies, colleagues who help us perform the additional tests, and the TUE assessors. A TUE is not a mere formality, and a submission involves a lot more than simply completing the form. It is a serious, official application for permission to use a particular medication, and must be properly completed and well justified. Additional tests conducted by various professionals must be attached, the results of which may not always be as desired,<sup>8</sup> the application sections listed above must be addressed in detail, and the official form must also be completed. In short, the application requires quality work and plenty of time. It must also be emphasized that a TUE application is not a document that should be submitted "just in case" or processed because

the word is out that "these medications can give positive doping results". Medications for asthma and other diseases may either constitute doping or not or they may under certain conditions result in an adverse analytical finding. All applications are evaluated by all members of the Therapeutic Use Exemption Committee (TUEC) of the Spanish Agency for the Protection of Health in Sport, a process which involves the dedication of several individuals and specific administrative procedures. The TUEC does not judge the treatments *per se*, but it does evaluate if the application for the use of that treatment, endorsed by a medical specialist, meets the criteria to permit the athlete to use a prohibited substance that, while allowing them to train and compete in health conditions similar to their peers on a level playing field, might also enhance their performance.<sup>9</sup> However, this standard of quality is not always achieved. As shown in Table 1, a total of 465 applications were made in 2015, 131 (28.2%) of which were for beta-agonists, and of these, 61 (46.6%) were unnecessary. Furthermore, rectification was requested for 25% of the 69 applications for the use of terbutaline, in the form of a request for a more comprehensive report or for a better rationale, particularly regarding points 2 and 3 mentioned previously. We would draw attention to this, since point 3 requires the most justification, in view of the availability of alternative treatment, and point 4 is the criterion which allows the use of some bronchodilators, but under the terms of a TUE.<sup>10,11</sup> With regard to the overall number of applications for the use of corticosteroids in the context of asthma, nearly all are unnecessary, since they refer to permitted treatments and routes of administration. In summary, of the 202 applications related with the treatment of asthma submitted by pulmonologists, allergologists, pediatricians, family doctors, and sports physicians, 132 (65%) were unnecessary, and 21 (10%) had to be rectified. We can surely do better than that.

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1579-2129/

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## Pulmonary Mycobacteriosis in a Patient Receiving Chronic Methotrexate Treatment<sup>☆</sup>



### Micobacteriosis pulmonar en un paciente en tratamiento crónico con metotrexato

Dear Editor,

We report the case of a 42-year-old man, Dutch national, resident in Spain for 11 years. He was an active smoker with a cumulative pack-year index of 15, and no other toxic habits, and reported no use of saunas or hot tubs. He had a diagnosis of pityriasis lichenoides, treated with 7.5 mg methotrexate weekly for the previous 5 years. He attended the emergency department with a 2-week history of 38 °C fever, myalgia, cough, expectoration of mucus, and dyspnea on moderate exertion. Initial clinical laboratory results showed 11,190 leukocytes/mm<sup>3</sup> (70% neutrophils, 19% lymphocytes, 9% monocytes), C-reactive protein 11.2 mg/dl, and procalcitonin 0.56 ng/ml. Arterial blood gases were FiO<sub>2</sub> 0.24, pH 7.48, PaCO<sub>2</sub> 37 mmHg, PaO<sub>2</sub> 87 mmHg and HCO<sub>3</sub> 27 mmol/l. Chest X-ray revealed bilateral consolidations in the middle and lower fields. Urine antigen testing was negative for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup-1, and nasopharyngeal swabs for H1N1 virus, sputum smear microscopy and HIV serology were also negative. Community-acquired pneumonia with Fine score III<sup>1</sup> in an immunosuppressed patient was suspected, so antibiotic therapy with ceftriaxone and levofloxacin was started, and the patient was admitted to the respiratory medicine ward. Three days after admission, the patient's fever persisted with no clinical improvement, so the first bronchoscopy was performed, revealing a predominantly mononuclear cell count in the bronchoalveolar lavage (BAL): 58% macrophages, 60% lymphocytes, 3% neutrophils. Only adenovirus was identified by polymerase chain reaction (PCR), so cidofovir was added to the treatment. One week after hospitalization, the patient's failure to improve clinically and radiologically prompted the performance of a chest computed tomography (CT) which confirmed consolidation in both lung bases (Fig. 1A), so a second bronchoscopy was performed and a transbronchial biopsy

was obtained. Tests for anti-nuclear and anti-neutrophil cytoplasmic antibodies, rheumatoid and angiotensin-converting enzymes were all negative. Two days later, the patient presented clinical worsening with progressive consolidation and high oxygen requirements (PaO<sub>2</sub>/FiO<sub>2</sub>: 97 mmHg), so he was transferred to the Intensive Care Unit for monitoring and administration of high-flow oxygen therapy. Standard cultures of both bronchial aspirate and BAL grew saprophytic flora, and the sputum smear, galactomannan and study of viruses and parasites were all negative. BAL cytology showed persistent predominance of mononuclear cells. Transbronchial biopsy revealed non-necrotizing granulomas (Fig. 1B). Mycobacterial infection was suspected, although other etiologies such as sarcoidosis or pneumonitis associated with methotrexate could not be ruled out. Standard anti-tuberculosis treatment and methylprednisolone (1 mg/kg/day) were started. PCR testing (Real-Cycler TBM, Molecular Progeny) for *Mycobacterium tuberculosis* detection in BAL and the biopsy specimen was requested, both of which were negative. Having ruled out tuberculosis, a PCR was performed for non-tuberculous mycobacteria (NTM) (INNO-LIPA *Mycobacteria* v2, Innogenetics) on the first BAL sample, in which *Mycobacterium intracellulare* (*M. intracellulare*) and *Mycobacterium simiae* (*M. simiae*) were identified. Treatment was switched to rifampicin, ethambutol, azithromycin, and moxifloxacin, and rapid tapering of the corticosteroids began. Clinical and radiological improvement was observed, with oxygen saturation of 94% breathing room air at discharge. No microbiological confirmation was obtained from mycobacterial cultures in any of the respiratory samples tested. The patient continued treatment for 1 year, and remained asymptomatic with practically complete resolution of radiological changes.

The worldwide incidence and prevalence of pulmonary disease caused by NTM is increasing. It affects both immunosuppressed and immunocompetent individuals<sup>2</sup>; in our case, a patient receiving chronic treatment with methotrexate.

With regard to the mycobacteria identified in our patient, *M. simiae* is rarely associated with lung disease, suggesting that its isolation is due to environmental contamination.<sup>3</sup> Indeed, pseudo-outbreaks caused by contaminated hot water supplies have been reported.<sup>4</sup> Most cases have been described in the southern United States, Cuba, and Israel.<sup>3–5</sup> Affected patients are primarily elderly immuno competent individuals with underlying lung disease, but disseminated infection can also occur in patients

<sup>☆</sup> Please cite this article as: Dal Molín-Veglia MA, Sánchez-Martínez F, Fernández-Alarza AF, Domínguez-Álvarez M. Micobacteriosis pulmonar en un paciente en tratamiento crónico con metotrexato. Arch Bronconeumol. 2018;54:225–226.