

# Triamcinolone Acetonide in the Treatment of Corticosteroid-Resistant Asthma: Risks and Benefits

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**Few therapeutic alternatives to prednisone are available for severe, corticosteroid-resistant asthma. Injectables triamcinolone acetonide (TA) has been used in this type of asthma, although its use is controversial. TA shows considerable efficacy when compared with prednisone according to nearly all studies, although the majority do not provide a high level of evidence. The use of TA has been questioned, with claims put forward that it is equivalent to increasing the corticosteroid dose, thus leading to a higher risk of adverse effects. This would mean that TA would not represent an improvement over prednisone because of the trade-offs between risks and benefits. This interpretation is questionable, however, because the data show that TA causes fewer adverse effects than prednisone, meaning that the balance of risks and benefits does favor TA. Therefore, TA can be considered a useful option for the treatment of patients with severe prednisone-resistant asthma.**

**Acetónido de triamcinolona en el tratamiento del asma resistente a los glucocorticoides: riesgos y beneficios**

**Las alternativas terapéuticas a la prednisona en el asma grave que no responde a los corticoides son escasas. El acetónido de triamcinolona (AT) de administración inyectada se ha utilizado en esta asma, aunque su empleo es motivo de controversia. Casi todos los estudios realizados, aunque en su mayoría son de escasa calidad, muestran una eficacia sustancial del AT comparado con la prednisona. Se ha cuestionado el uso del AT aduciendo que equivale a aumentar la dosis del glucocorticoide, lo que comportaría un mayor riesgo de efectos secundarios, de modo que el balance final de riesgos y beneficios del AT no mejoraría el de la prednisona. Los datos publicados permiten dudar de esa interpretación, ya que muestran que el AT ocasiona menos efectos secundarios que la prednisona, por lo que el balance de riesgos y beneficios es superior al de esta última. Por ello puede considerarse el AT una opción válida para tratar a los pacientes con asma grave que no responde a la prednisona.**

**Key words:** Severe asthma. Corticosteroid-resistant asthma. Prednisone. Triamcinolone acetonide.

**Palabras clave:** Asma grave. Asma corticorresistente. Prednisona. Acetónido de triamcinolona.

## Introduction

The therapeutic response of asthma to corticosteroids is highly variable: some patients respond to low doses of an inhaled corticosteroid whereas others experience no response even at high doses administered systemically, a condition known as severe corticosteroid-resistant asthma or refractory asthma. Corticosteroid resistance itself also varies in severity, ranging from minimal response at high doses of oral corticosteroids to virtually no improvement with the same treatment.<sup>1</sup> Failure to respond to corticosteroids has been related to various hormone receptor abnormalities.<sup>2,3</sup>

Corticosteroid-resistant asthma affects a small percentage of asthma patients, but is a relatively common challenge for the physicians who work in the hospitals to which these patients are usually referred. The poor quality of life and the risks involved with high-dose systemic corticosteroid therapy (which also provides few therapeutic benefits) are an ever-present problem for physicians who treat corticosteroid-resistant asthma.

Many cases of severe refractory asthma are in fact known to be "false" severe asthmas. A number of factors should be investigated in patients with severe disease, including poor therapeutic compliance, other obstructive upper airway or generalized lower airway diseases, associated functional dyspnea, and possible comorbidities, since they may contribute to poor response to treatment.<sup>4</sup>

Numerous therapeutic options (including methotrexate, gold salts, and cyclosporine) have been tested in severe asthma. These treatments have had poor results and have also led to severe systemic adverse effects.<sup>1</sup> More recently, the introduction of omalizumab, a monoclonal antibody targeting immunoglobulin E, has led to improved control

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in a relatively large number of these patients, although its use is presently restricted to severe corticosteroid-dependent asthma with a proven allergy trigger, a situation found only in a low percentage of patients with this type of asthma at this time.<sup>5</sup>

### **Triamcinolone Acetonide in the Treatment of Severe Corticosteroid-Resistant Asthma**

The literature contains many studies on the use of slow-release preparations with triamcinolone acetonide (TA) in the treatment of severe corticosteroid-resistant asthma.<sup>6-14</sup> The majority of studies do not provide a high level of evidence, however: only 2 double-blind placebo-controlled studies have been published<sup>12,14</sup> and all others have been open studies with few patients. The studies on TA reveal enormous variation in the use (both in dosages and dosing intervals) and follow-up time. Several have analyzed the results of a single 40-mg to 60-mg dose of TA<sup>6,7,12</sup> or a 40-mg dose repeated 3 times,<sup>6</sup> others have analyzed the effects of a single 120-mg or 360-mg dose of TA,<sup>13,14</sup> and still others report on patients treated between 4 months<sup>10</sup> and 2 years or more<sup>11</sup> with changing doses of TA administered at time intervals that have varied according to the course of the symptoms.<sup>5</sup>

#### *Clinical Efficacy*

TA efficacy is generally assessed based on the improvement in clinical symptoms, decrease in bronchial obstruction (measured by serial peak expiratory flow determinations or forced spiroometry), and impact on severe acute exacerbations and hospital admissions. The results with TA are compared with previous results with prednisone or prednisolone. All published studies in patients who presented severe, persistent unstable asthma treated with high-dose prednisone or prednisolone have described positive responses to TA in terms of symptoms and bronchial obstruction.<sup>5-13</sup> Clinical efficacy is also evident in the lower number of hospital admissions and the preferences of patients who, when questioned about the results achieved with TA, did not hesitate to describe them as superior to those of prednisone.

The outcome measures in 2 studies were inflammatory markers: exhaled nitric oxide in one<sup>7</sup> and eosinophil count in induced sputum in the other.<sup>11</sup> Extremely positive effects on inflammation were observed in both. In the study investigating sputum eosinophilia, TA treatment achieved a significant reduction in sputum eosinophil count in patients in whom prednisone failed to do so.<sup>11</sup> TA is not only effective in eosinophilic asthma. As was seen in the other study, patients with sputum neutrophilia also responded well to TA treatment.<sup>7</sup>

Because those studies do not use the same doses and dosing times, sufficient information cannot be compiled to establish the dose-response relationship with certainty. However, the limited data available in this regard appear to suggest that higher doses yield a better clinical response, greater reduction in bronchial obstruction, and larger decrease in the number of exacerbations and hospital admissions.<sup>6,13,14</sup>

Several studies have reported that the therapeutic action of an intramuscular injection of TA has a mean duration of 4 to 5 weeks, although this period may vary between patients and even within the same patient treated for months or years when injection frequencies change according to the course of the illness.<sup>5</sup> The study analyzing the effect of TA on exhaled nitric oxide showed that the therapeutic effect lasted 4 to 5 weeks in most cases, and that worsening of inflammation preceded the onset of clinical deterioration.<sup>7</sup> In patients treated with high doses of TA (120-360 mg), the therapeutic efficacy seems to last longer than 5 weeks.<sup>13,14</sup>

It is unclear why TA is effective when prednisone fails, although several possibilities have been proposed: *a)* the use of injections improves therapeutic compliance; *b)* the intramuscular route is more effective than the digestive route, or *c)* the pharmacological characteristics of TA contribute to its good results. Although therapeutic compliance may partly explain some of the success with TA therapy, it does not appear applicable to most published cases, in which it was apparent, in view of the adverse effects detected, that patients were using prednisone regularly or frequently. Regarding parenteral administration, no well-founded arguments have been put forward to explain the greater efficacy of that route over oral administration; in fact, several trials have failed to show that the mode of administration influences the therapeutic results of corticosteroids.<sup>15,16</sup> Thus, the third explanation referring to the pharmacological properties of TA appears to be most plausible. After intramuscular injection, peak plasma concentration is reached within 8 to 48 hours, followed by a gradual decrease in drug concentrations to undetectable levels around day 21.<sup>17</sup> Conversely, oral prednisone is rapidly absorbed through the digestive mucosa, then metabolized in the liver and converted into prednisolone, its active metabolite. Prednisone has a plasma half-life of 1 to 2 hours and a biological half-life of 18 to 36 hours.<sup>18</sup> The fact that the therapeutic efficacy of TA lasts about 4 weeks suggests a direct relationship to the pharmacological properties described. The permanent presence of the corticosteroid in the tissues may allow continued exposure of inflammatory cells to the drug, in comparison with the short, intermittent exposure achieved with prednisone, an aspect which might make TA more effective. However, these interpretations are mere speculations that have not been demonstrated in any studies.

#### *Adverse Effects*

The use of corticosteroids is limited by a number of known systemic adverse effects, such as osteoporosis, glaucoma, skin atrophy, muscle disease, menstrual cycle disorders, and adrenal function abnormalities. One of the criticisms of TA use instead of prednisone is that it merely replaces one drug with another administered at higher pharmacological doses. This results in greater therapeutic efficacy but has the drawback of more serious systemic adverse effects.<sup>19</sup> Whenever the adverse effects of 2 drugs are compared, pharmacological doses of equivalent potency should be used. However, this approach is difficult in drugs

with such widely disparate characteristics as prednisone and TA. Additionally, it is not uncommon to change drug doses often in severe, unstable asthma. Therefore, in some studies, it may be difficult to establish the proper time to assess adrenal function. The pharmacokinetics of TA are complex, making it hard to choose the right moment to analyze its effects on the adrenal glands for comparison with prednisone.

The analysis of other adverse effects of corticosteroid treatment that are readily quantifiable, such as body weight and blood pressure, appears to be more feasible.<sup>10,11,13,14</sup> Changes in the external signs inherent in Cushing's syndrome (moon face, stretch marks, hirsutism), muscle strength and atrophy (muscle disease), and cutaneous lesions (thinning of the skin and bruising due to capillary fragility) have also been used.<sup>10,11,13,14</sup>

Although with some discrepancies, most studies that have performed some kind of adverse effect assessment have shown favorable results for TA,<sup>10,11,13</sup> except for skin and menstrual cycle abnormalities.<sup>11,14</sup> Thus, TA has been shown to improve compromised adrenal function,<sup>6,13</sup> favoring weight loss, normalization of blood pressure, and reductions in the external signs of hypercortisolism (moon face).<sup>10,11,13</sup> In some studies, hirsutism was observed more often among patients treated with TA compared with prednisone.<sup>11,14</sup>

TA therapy appears to cause more adverse effects on the skin than prednisone. Thinning of the skin and bruising that occurs spontaneously or after small injuries (for instance, simple rubbing against a blunt surface) are the most common complications of TA therapy. On occasions, small skin wounds become lesions that take a long time to heal and leave disproportionately large scars for the severity of the injury and the initial lesion (unpublished observation).

Why does TA have a more favorable profile than prednisone in some adverse systemic effects (weight, hypertension, cushingoid facies) and a less favorable one in cutaneous effects? The frequency and importance of skin involvement may be related to the fact that TA is a fluorinated compound, given that all corticosteroids of this type administered by any route (topical, inhaled, systemic) commonly lead to skin lesions.<sup>20,21</sup> Nevertheless, little information is available on the mechanisms by which TA can induce adverse effects of contrasting severity according to the tissues and systems affected.

#### Risk-Benefit Balance

The decision to switch away from a drug that has proven relatively ineffective in the treatment of a certain disease depends on whether the risk-benefit balance favors the new drug over the drug being replaced. The decision should be based on information from trials conducted under reliable conditions, namely, a double-blind design, with a sufficient number of patients, and the use of adequate tests to assess efficacy and adverse effects. These conditions are not present in the studies carried out to compare TA with prednisone. Only 2 of them had an appropriate design, but were limited by a low number of patients and very short course of treatment.

Naturally, the paucity of scientific data hinders an in-depth assessment of the risks and benefits of TA in the treatment of severe prednisone-resistant asthma. Despite this shortcoming, the available published data appear to show that TA use may be justified in patients with severe, unstable asthma receiving regular prednisone treatment because it is more effective and has fewer adverse effects in general than prednisone. The balance of risks and benefits is thus favorable for TA.

Interestingly, intraocular TA injection has proven to be effective for treating prednisone-resistant diabetic retinopathy. As in the case of asthma, this observation has stirred up a lively debate on its use for this purpose, on possible explanations for its efficacy, and on the risk-benefit ratio for such use.<sup>22</sup>

#### Conclusion

Few therapeutic alternatives to prednisone are available for severe, unstable, corticosteroid-resistant asthma. Injectable TA has occasionally been used in this type of asthma. The available medical literature shows that TA is much more effective and usually causes fewer adverse effects than prednisone and, therefore, the risk-benefit balance appears to be superior for TA as compared to prednisone. Thus, TA can be considered a useful option for treating patients with severe, unstable asthma with little or no response to prednisone. Nevertheless, long-term, double-blind trials comparing TA and prednisone should be conducted to provide more support for the use of TA in severe, unstable asthma refractory to oral corticosteroids.

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