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Allopurinol: Attention to the Prescription!

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ABSTRACT

Allopurinol is a commun hypo-uricemic drug. However, it is main drug reported to be inducing toxidermy. Our goal is to encourage limiting the prescription of this drug and to reserve it for justified cases after some observations. A Retrospective study was conducted in the Dermatology department between 2012 and 2019. We collected all toxidermy cases following Allopurinol. During the study period,39 cases of severe Allopurinol toxidermia, including 22 women and 17 men, a sex ratio of 0.77. The average age was 65 years old. Most of the patients were "poly-medicated". The average time between medication and clinical symptoms was 28.25 days. Clinical manifestations were: macula-papular rash in 12 cases (30%), erythroderma in 14 cases (35%), purpura in 7 cases (17%) and mucosal involvement in 20 cases. Fever in 29 cases, a state of shock in 5 cases. 10 patients required a transfer in intensive care. On the balance sheet; eosinophilia was found in 23 cases, 18 cases of hepatic cytolysis, CPK mb was elevated in 17 cases, acute renal failure in 24 cases. The biopsy was performed in all cases confirming the toxidermy. The Drug reaction eosinophilia and systemic symptoms (DRESS) retained in 29 cases, Stevens-Johnson syndrome (SJS) in 2 cases, Lyell in 4 cases. The management involved stopping the incriminated drug (Allopurinol) and the introduction of an antihistamine and an emollient were prescribed in all patients. Topical steroid in 21 patients. Oral corticosteroid therapy in 14 patients. A bolus of corticosteroid was administered in 4 patients. The evolution was good for 30 patients (77%). However, we recorded 9 deaths in a context of septic shock and multi-visceral failure. In our series, Allopurinol was the cause of severe toxidermia including Lyell syndrome, Stevens-Johnson and DRESS syndrome. The severity of these diseases should encourage preserving it for the justified cases, and knowing how to adapt the dosage to the renal function, to introduce the treatment in a progressive way and to stop the treatment in case of less signs of toxidermy. The control of the use of this molecule would reduce the cases of this disease.

KEYWORDS

Toxidermia; Allopurinol; DRESS; Drug

1. INTRODUCTION

Allopurinol is a xanthine oxidase inhibitor mainly used in the management of gout. It is a drug that has been marketed for over 40 years on the market [1,2]. It is also one of the main drugs inducing sever toxidermia such as Lyell syndrome, Stevens - Johnson syndrome (SJS), and DRESS Syndrome (drug reaction with eosinophilia and

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systemic symptoms). These drug reactions may be life-threatening.

The aim of our work is to raise the importance of reserving this medication for justified cases and to remind treating physicians of the obligation to respect the indications and follow-up treatment in order to avoid these serious undesirable effects.

2. MATERIALS AND METHODS

We performed a retrospective study of the clinic, laboratory and following profiles of all cases of Allopurinol toxidermia; hospitalized in the department of dermatology and venereology of Hassan II University Hospital of Fez in Morocco, over a period of 11 years from January 2009 to September 2019. Our department is one of the largest teaching units in Morocco, integrated into a tertiary school, it is a reference hospital in the central region of the country.

3. RESULT

We collected 39 cases of severe Allopurinol toxidermia, including 22 women and 17 men, with a male to female ratio of 0.77. The average age was 65 years old. Allopurinol has been prescribed in all patients for hyperuricemia with or without manifestations of gout. Most of the patients were "poly-medicated". The average time between medication and clinical symptoms was 28.25 days. Clinical manifestations were: Maculopapular rash in 12 cases (30%), erythroderma in 14 cases (35%), purpura in 7 cases (18%) and mucosal involvement in 20 cases (51%). The fever in 29 cases (74%), a state of shock in 5 cases (12%). 10 patients required transfer to intensive care (25%). In the laboratory abnormalities; we noted an eosinophilia in 23 cases (58%), 18 cases (46%) of hepatic cytolysis, creatine phosphokinase (CPK mb) was elevated in 17 cases (43%), acute renal failure in 24 cases (61%). The biopsy was performed in all cases confirming the toxidermia. The DRESS syndrome retained in 29 cases (74%), SSJ in 2 cases, Lyell in 4 cases.

The management involved stopping the incriminated drug (Allopurinol) and the introduction of an antihistamine and an emollient were prescribed in all patients. Topical steroid in 21 patients (53%). Oral steroid therapy at a dose of 0.5 mg/kg/day - 1 mg/kg/day in 14 patients (53%). A bolus of corticosteroid was administered in 4 patients (0.1%).

The evolution was good for the majority of our patients (30 patients or 76%) with a clinico-biological improvement obtained on average after 15 days of hospitalization. However, we recorded 9 cases of deaths occurred in a context of septic shock and multi-visceral failure.

4. DISCUSSION

Allopurinol is the first xanthine oxidase inhibitor to be marketed more than 40 years ago [1]. It is an anti-drip with usual prescription; It constitutes the reference treatment of symptomatic hyperuricemia [2]. It is generally well tolerated. However, it is the leading cause of severe bullous toxidermia in Europe and is one of the leading providers of DRESS Syndrome worldwide [2].

These drug reactions appear to be more frequent in "poly-medicated" patients and this frequency of drug combination is aggravated by self-medication [3].

The physiopathological mechanisms and the risk factors for the occurrence of these serious toxidermias are only partially known, although they are widely described in the literature. The likely role of the HLA-group has been reported in several pharmaco-genetic studies showing that, in Asian populations, HLA-B5801 is found in 80% - 100% of patients with bullous toxidermia under allopurinol compared with only 9% - 15% in the general population [4-12]. High doses of allopurinol favoring

toxidermias have recently been confirmed by a comparative study with a significantly higher daily dose of allopurinol in patients with bullous toxidermia compared to allopurinol-tolerant patients [5]. Oxypurinol is largely eliminated by the kidneys. The accumulation of oxypurinol in the body is related to the half-life, depends on the renal function. Thus, in people with normal renal function, oxypurinol has a half-life of about 18-30 h. However it can reach a week in people with severe renal impairment [6]. Pre-existing renal insufficiency or co-prescription of thiazide diuretics is also incriminated in the occurrence of severe allopurinol toxidermias, explained by the hyper-uricemic effect of diuretics leading to a higher probability; than in the general population; of allopurinol in these patients demonstrated in a european comparative study conducted in 2008 [7].

Drug reaction with eosinophilia and systemic symptoms or DRESS occurs in 2% of patients treated with allopurinol [8]. It is a rare but severe idiosyncratic reaction [9]. 74% of our patients had a DRESS syndrome. Systemic attacks of this pathology are severe and can compomise the vital prognosis in 10% of cases by severe sepsis [9], by renal or hepatic impairment. Lyell is the most serious form of toxidermias, it is a diagnostic and therapeutic emergency in dermatology and responsible of 20% of mortality [3]. 10% of our patients presented a Lyell. In our series, 23% of our patients have died, secondary to septic shock and multi-visceral failure. For all types of toxidermias.

The misuse of allopurinol as well as the persistence of reports of serious cutaneous adverse reactions led the National Agency for the Safety of Medicines and Health Products in France (ANSM) to a retrospective analysis of observations reported in the national system of pharmacovigilance for a period of three years (2008-2010). This analysis has highlighted [10-11].

Firstly, that a high incidence estimated at an average of 1 case for 2000 new patients treated, allopurinol toxicities (including Lyell, Stevens-Johnson and DRESS syndromes) occurring most often during the first two months of treatment, sometimes with fatal outcome. which joins the data of our series where the average time between medication and clinical symptoms was 28.25 days. Concerning female predominance, it was the same in our study. Secondly, it was noted failure to comply with the recommendations for adjusting the dosage to renal function in approximately half of the cases. Thirdly, it was demonstrated Link between high doses and the risk of serious toxidermias. Fourthly, it was remarked a Frequent off-label use and finally, it was mentioned delayed management due to a lack of knowledge of its risks by health professionals and patients

As a result of this analysis, 60% of reported cases were found to be preventable due to an unjustified indication.

The occurrence of severe toxidermia is secondary to the lack of understanding of dosage adjustment and adherence to Allopurinol indications by prescribers, has been demonstrated in several studies.

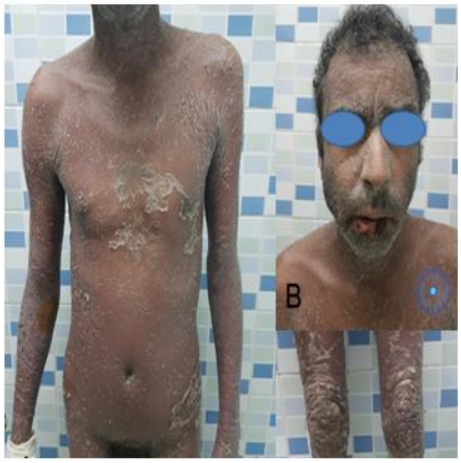

Figure 1: Erythroderma during a DRESS syndrome.

The severity of allopurinol-induced toxidermia should encourage clinicians to maintain it for justified cases, to adjust the dosage for renal function, to introduce

treatment gradually and to discontinue treatment at the slightest sign of adverse effects (Figure 1 & Figure 2).

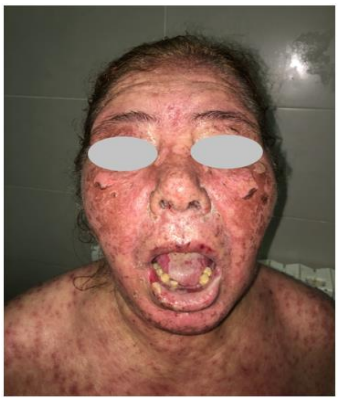

Figure 2: Severe mucosal involvement with skin abruption during SSJ.

5. CONCLUSION

Allopurinol is an effective and inexpens ive drug. However, it is responsible of several cases of serious and potentially life-threatening toxidermia. The control of the use of this molecule and the understanding of prescribing rules by clinicians, could avoid the cases of toxidermia and prevent death.

6. CONFLICTS OF INTEREST

The authors do not declare any conflict of interest.

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