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IMPLEMENTING PHARMACOVIGILANCE THROUGH PHARMACEUTICAL CARE: A THREE-MONTH PILOT STUDY WITH PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Diseases related to the immune system have seen their incidence grown in the latest years and Systemic Lupus Erythematosus (SLE) is not the exception. Pharmacological treatments include several immunosupressants and other drugs which expose patients to an ample variety of Drug Related Problems (DRPs) and Adverse Drug Reactions (ADRs). This study aimed to determine the incidence and type of ADRs among patients with SLE of the Autoimmune Disease Clinic in the University Hospital of Uruguay following the implementation of a Pharmaceutical Care Programme. During a 3-month study, 13 women, aged 21 to 67 years old, were included. DRPs were classified according to the Second Consensus of Granada. ADRs were categorized using the WHO severity grading scale for ADRs and attribution of causality was assessed using Naranjo´s algorithm. Twenty-five DRPs were detected, 15 of them in the safety category, Hydroxychloroquine was the drug commonly involved in ADRs. Fatigability and rash were the ADRs the patients complained the most. Three patients on hydroxychloroquine and prednisone referred visual disturbances. Rash and visual disorders were categorized as moderate or severe according to the WHO severity scale. The rest of the ADRs were classified as mild. All ADRs were notified using the National Form for ADRs. Pharmacists Interventions were handed out to treating physicians and written information was given to

patients. Performing active pharmacovigilance in SLE patients showed that ADRs in this population are not negligible, and that pharmacists play a key role contributing to better patient care and improving ADRs notification.

KEYWORDS: Systemic Lupus Erythematosus, Adverse Drug Reactions, Active Pharmacovigilance.

INTRODUCTION

Several diseases related to the immune system have seen their incidence grown in the latest years probably due to the fact that there is a stress related factor that underlies their instauration. Among these, Systemic Lupus Erythematosus (SLE) is an example.

SLE has a reported prevalence of approximately 20 to 150 cases per 100,000 in the population.[1] Women present higher rates compared to men (7:1). Among women, blacks had a higher prevalence of lupus by 2.5 to 3.5-fold compared to whites and Asian women appeared to have the lowest prevalence of SLE.[1] The early detection of the mild disease has nearly tripled the incidence in the last 40 years of the 20th century.[2]

SLE detection is difficult to perform due to the wide array of clinical manifestations it presents with, including rash, arthritis, anemia, thrombocytopenia, nephritis, fatigability, seizures and psychosis. This heterogeneous presentation usually delays diagnosis and may complicate treatment and prognosis. Morbidity and mortality may be also related to problems in access to care, less effective treatments, and poor compliance with therapeutic regimens.[3]

Treatments primarily consist of immunosupressants: hydroxychloroquine, corticoids (prednisone), azathioprine, micophenolate mofetil and cyclophosphamide.[3]

Patient´s compliance is often a problem, given the use of these medications which result in side effects in young, reproductive age women who want to partner and have children. This is a relatively unique demographic/therapeutic problem among the rheumatic diseases. Owing to the fact that pharmacotherapy is fundamental, aiming to diminish SLE flares and regression, pharmacotherapy follow-up may be crucial to reinforce adherence and prevent adverse events.

A Drug Related Problem (DRP) is an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome.[4] According

to the committee of the Second Consensus of Granada on Drug Therapy Problems, DRPs could be classified into three groups: necessity problems (when the patient makes use of an unnecessary medication, or when he/she does not utilize a necessary medication); effectiveness problems (when the utilized medication does not promote the desired effect, being it or not a dose-dependent result); safety problems (when the patient utilizes a medication that is not being safe, either due to utilization of a very high dose, or thanks to appearance of adverse reactions, irrespectively of the utilized dose and mainly due to interactions).[5] Pharmaceutical Care aims to eliminate or reduce DRPs including adverse drug reactions (ADRs). Active ADRs surveillance and spontaneous reporting are effective methods of pharmacovigilance but severe under-reporting is the major limitation of the latter and our country does not escape from this reality. It is vital to understand that Pharmacovigilance is an integral part within Pharmaceutical Care which is directly related to patient-centre outcomes.

This study therefore, aimed to determine the incidence and type of ADRs among patients with SLE of the Autoimmune Disease Clinic in the University Hospital of Uruguay following the implementation of Pharmaceutical Care under the technical leadership of the University Hospital Pharmacists and the Clinical Pharmacy Programme of the Pharmaceutical Sciences Department of the Faculty of Chemistry.

PATIENTS AND METHODS

The study was performed in the University Hospital, *Hospital de Clinicas "Dr. Manuel Quintela",* from September to December 2014. In this period 13 women (aged between 21 and 67) diagnosed with SLE were included in the Pharmaceutical Care Service of the Pharmacy. In all cases, inclusion was performed by the treating physician. Patients were interviewed in the pharmacy office to gather personal data, health problems, pharmacological treatments and medicinal plants commonly used. All data was registered in a form specially designed for this purpose. Clinical history was also consulted to check laboratories tests. DRPs were classified according to the Second Consensus of Granada. Pharmacists also recorded the suspected ADRs cases on the national yellow form, categorizing them as mild (grade I), moderate (grade II), severe (grade III), or life threatening (grade IV), according to the WHO severity grading scale for ADRs.[6] Attribution of causality was assessed using Naranjo´s algorithm.[7] After DRPs detection, mainly safety problems, intervention strategies were designed to solve them.

RESULTS AND DISCUSSION

Ten of the 13 patients (77 %) were polymedicated, which is not common in a group composed mostly by patients under 65. This fact should not be disregarded because polymedication makes patients more susceptible to DRPs.

During the pilot study period 25 DRPs were detected. More than half of DRPs (15) fell into the safety category. Of the 13 patients studied none presented effectiveness problems. Hydroxychloroquine was the drug that caused more safety DRPs. Absence of calcium carbonate and vitamin D in the therapy of 3 patients on prednisone were categorized as necessity DRP. The use of medicinal plants was also classified as necessity DRP, because the patient consumed a possible therapeutic agent which was not prescribed by the physician.

Five of the thirteen patients (38 %) used medicinal plants, 2 consumed *Aloysia citriodora Palau* (Cedrón, as common name in Spanish), 1 *Achyrocline satureioides (*Marcela, as common name in Spanish), 1 was with *Aloe Barbadensis Miller* (Aloe Vera, as common name in Spanish) and 1 was on two plants: *Gingko Biloba* and *Tilia platyphyllos* (Tilo, as common name in Spanish).

Potential pharmacodynamic interactions between medicinal plants and pharmacological treatment could be detected in two cases. One patient was on acetylsalicylic acid (100 mg/day) and *Gingko Biloba*, the latter is popularly used for cognitive deterioration but ginkogolide B and flavones present in its extracts have shown antiplatelet and anticoagulant properties.[8] Therefore, the co-administration of *Gingko Biloba* and acetylsalicylic acid could cause a possible ADR.

Another patient who was on prednisone (5 mg/day) also consumed *Aloe Vera* syrup. Prednisone produces potassium depletion because of its mechanism of action, and *Aloe Vera* has a purgative effect which may lead to diarrhea and loss of potassium on continued use. Due to hypertension with proteinuria, this patient also received losartan and enalapril, which may produce the opposite effect, hyperkalemia. Not only was this situation informed to the physician encouraging the determination of potassium serum levels, but also a warning of drug duplicity was given, to alert on the use of angiotensin converting enzyme inhibitors (enalapril) and an angiotensin II receptor blocker (losartan) concomitantly.

The use of medicinal plants is deeply ingrained in our population and the misconception that

natural products are innocuous raise the need for clear and scientific information which targets both patients and health professionals. In the two cases presented above written information was handed out to patients and physician to make them aware of plant-drug interactions.

The reported ADRs (safety DRPs) included fatigability (69.2%), rash (69.2%), visual alterations (23%), muscular pain (23%), tachycardia (7.7%) and mouth dryness (7.7%). The occurrence of ADRs has association in most cases with concomitant medicines and the pathology itself. Therefore, when attribution of causality was assessed using Naranjo´s probability scale most of ADRs resulted possible except for mouth dryness. Table 1 presents ADRs distribution according to drug and the probability score.

Table 1. Description of ADRs reported, possible drug related and probability assessment.

ADR	Drug/Associated Drugs	Total	Probability
Fatigability	Hydroxychloroquine	9	Possible
Rash	Hydroxychloroquine	8	Possible
Rash	Hydroxychloroquine/mycophenolate of mofetil	1	Possible
Visual alterations	Hydroxychloroquine/prednisone	3	Possible
Tachycardia	Amitrityline/levothyroxine	1	Possible
Muscular pain	Vitamina D	2	Possible
Muscular pain	Vitamin D/alendronate	1	Possible
Mouth dryness	Amitriptyline	1	Probable

Visual disorders and rash could be classified according to WHO-Adverse Reaction Terminology as moderate or severe (grade II or III). The rest of the ADRs were classified as mild (grade I).

Evidently, hydroxychloroquine was the drug which caused most ADRs, which included fatigability, rash and visual alterations. Even though fatigability and rash may be provoked by lupus itself, patients noticed a worsening of these symptoms once hydroxychloroquine was incorporated in the treatment. Visual problems could be an imminent problem in lupus treatment. The three patients that complained of visual disturbances were taking two possible medications responsible for this adverse effect: hydroxychloroquine and prednisone. It is well-documented in the literature the hydroxychloroquine-induced ocular toxicity.[9] Prednisone can also cause visual problems: elevated intraocular pressure and cataract

formation.[10] It is imperative that patients and physicians are aware of and watch for drug's ocular side effects. All ADRs were communicated to the treating physician through a pharmaceutical intervention and notified to the pharmacovigilance committee using the yellow form. The patients with visual disorders were derived to ophthalmological assessment. In the case of cutaneous reactions, only the treating physician together with a dermatologist could decide if it was the drug or drugs of the therapy or the worsening of the pathology.

An important issue to take into consideration is that the high prevalence of polymedication in this group places them at increased risk of suffering ADR therefore, prescription should be revised in a thorough, critic and structured manner.

CONCLUSIONS

Pharmacists are uniquely positioned to play a role in Pharmacovigilance which is an important component in any quality pharmacy services. Pharmacists deliver best drug therapy through Pharmaceutical Care and consequently, could positively contributed in better patient care by ensuring effective and safe use of drugs and improving ADRs notification.

All in all, the number of DRPs and ADRs detected in this study group was not negligible thus performing active pharmacovigilance in these patients through Pharmaceutical Care is a need.

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