Original Article

ASSESSMENT OF INJECTION SITE REACTION IN PATIENTS TREATED WITH BIOLOGIC DRUGS FOR SUBCUTANEOUS ADMINISTRATION

Yulitza Geomara Villamar-Torres[1], Vilma Rocío Quijije Chavez[2], Mariuxi Zurita Desiderio[3]

[1,2,3]Facultad de Ciencias de la Salud. Carrera de Enfermería. Universidad Técnica Estatal de Quevedo. Los Ríos, Ecuador.

Email: yvillamart@uteq.edu.ec

Abstract

The present study aimed to evaluate skin reactions associated with biologic drugs administered subcutaneously. It was conducted at the Fundació Hospital de l'Espèrit Sant, Barcelona, Spain. The study population was considered to be patients who had a monthly and maximum 12-week treatment with subcutaneous administration of biologic drugs. The variables studied were those related in the first part to the clinical history: age, sex and diagnosis of the patient, additionally, the names of the drug and frequency of use were considered. A clinical interview was conducted on the self-administration of the drug, for example: if hands were washed before the application of the drug, placed on the body where the drug was administered, rotations of the puncture site and reactions at the puncture site. Among the most relevant results, the mean age of the patients was 54 years, the sex that influenced was male with 50.5%, and a prevalent diagnosis of rheumatoid arthritis with 32%. The most commonly used drug was adalimumab 60% with a frequent regimen every 2 weeks with 43%. It was presented that 90% of the patients washed their hands before administration, the preferential puncture site reported was the abdomen with 73%, and the puncture site was rotated in 82%. It was obtained that 4 patients out of a total of 99 patients evaluated had puncture site reactions, three with the drug adalimumab in the thigh and abdomen area; and one with etanercept in the abdomen area. Since this was a pilot test, the present research suggests continuing to explore other investigations that allow elucidating more conclusively if there is a relationship between the drugs used and their adverse reactions.

Keywords: skin reactions, biologic drugs, rheumatoid arthritis.

INTRODUCTION

In 2008, the Spanish Agency for Medicines and Health Products (AEMPS) reported that 3 of the 10 best-selling drugs in Europe were biologics. However, five years later, this number increased considerably, with 8 of the 10 best-selling biologic drugs (28). Biological medicinal products are those containing one or more active ingredients, produced or derived, of biological origin. Some of these active ingredients are naturally (physiologically) present in the human body, for example, proteins such as insulin, growth hormone and erythropoietin.

Biologics act by modifying the host response to disease and include monoclonal antibodies and a variety of protein drugs that alter the activity of cytokines (such as interferons and interleukins), enzymes and growth factors (32). They differ from conventional chemical drugs, among others, in that they have a much higher molecular weight and complexity than products derived from purified or synthetic chemicals (1).

Address for correspondence: Yulitza Geomara Villamar-Torres
Facultad de Ciencias de la Salud. Carrera de Enfermería. Universidad Técnica Estatal de Quevedo. Los Ríos, Ecuador.
Email: ysrakhalaf78@tu.edu.iq

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There are different types of adverse reactions that appear at the time of subcutaneous administration of the drug where they are detected in routine clinical practice and clinical trials. These include the following: erythema, pruritus, edema at the puncture site, pain, swelling, extravasation and abscesses (4-5).

Considering the reactions at the injection site, clinical studies (22) show that some of the factors that influence the pathology are that some patients have an immediate type I hypersensitivity mediated by Ig; these are receptors of the membrane of mast cells and basophils of peripheral blood, which react 15 minutes after the administration of the drug.

Previous studies consider the influence of different factors, such as dietary habits or body fat distribution, on the injection site reaction to the use of immunomodulators in multiple sclerosis. However, scientific evidence on the factors that may influence this reaction after the administration of the biological drug is scarce (6). Currently, prefilled pens are one of the main pharmaceutical forms used in the administration of drugs subcutaneously and also in biologic drugs. Important aspects of the use of prefilled pens include the following. The pen is administered subcutaneously in the following areas: deltoid, abdomen or thighs and it is recommended to always rotate the puncture site. Remove the syringe from the refrigerator 15-30 minutes before administration so that it is at room temperature (26). To date, very little evidence has been reported on the assessment of injection site reactions in patients treated with subcutaneous administration of biologic drugs; therefore, the purpose of this research was to evaluate these reactions considering a finite population and as a pilot plan.

METHODOLOGY

Study design

The study was observational, longitudinal and retrospective, as a pilot plan due to the urgency of obtaining at least preliminary results for decision-making in future clinical cases.

Scope and period of the study

This research was carried out in the hospital setting and, specifically, at the Fundació Hospital de l'Espèrit Sant. This is a regional acute care hospital integrated into the Integrated Health System of Catalonia (SISCAT), which is located in Santa Coloma de Gramenet and supports hospital care in the Northern Metropolitan Area. Its reference center is the Hermanos Trias y Pujol University Hospital in Badalona and it also works in coordination with the Primary Care of Santa Coloma. It covers a population of about 220,000 people in the municipalities of Santa Coloma de Gramenet, Sant Adrià de Besós, Badalona (Llefià neighborhoods) and Barcelona (Buen Pastor neighborhood). The period of application of the surveys was from March 9 to May 9, 2016.

Study population and selection criteria

The population consisted of all the patients who attended during the duration of our study; it should be emphasized that these were patients who went to the pharmacy service to pick up the biological drug for subcutaneous administration with a minimum monthly frequency and a maximum frequency of 12 weeks, depending on the frequency of administration of their treatment, and who signed the written informed consent form. For this purpose, patients booked an appointment in the dispensing schedule of the pharmacy service, usually in the morning; patients scheduled in the afternoon were evaluated at the next appointment. The technical staff of the pharmacy service is in charge of dispensing the drugs.

The clinical interview was conducted at the time of dispensing the drug, explaining the study and facilitating the signing of the informed consent form by the patients who decided to participate in the study. The study presents a selection bias due to the exclusion criteria, because of time limitations for carrying out the study. For this reason, the study was only carried out taking as reference those patients with a frequency of administration of 12 weeks. It should be noted that in many cases it was a family member and/or caregiver who came to withdraw the medication and, in this case, the interview was not carried out.

Obtaining information

The data were obtained from two main sources: the patient's clinical history and by interview, for which it was necessary to previously design a survey through the clinical history, the following data were recorded:

* Sociodemographic variables: age, sex, 54

* Variables related to the disease: diagnosis

* Variables related to the drug: name of the biological drug used and frequency of use (also dosage).

*The following information related to the self-administration of the drug was recorded through a clinical interview with the patient and the survey: whether they washed their hands before applying the drug, the place of administration, and whether they rotated the puncture site. Collection of patients who have manifested reactions at the puncture site.

Information analysis

Once all the information had been obtained, we proceeded to analyze it. A descriptive analysis was carried out so that quantitative variables were expressed as mean and standard deviation and qualitative variables as frequency distribution.

RESULTS

Demographic variables

Figure 1 shows the total number of patients included during the study period, which was 99 patients. In addition, in some cases, several patients did not show up at the indicated appointment time to pick up the medication for personal

reasons and other patients presented a regimen that exceeded the 12 weeks of the study, the same, which is established in the inclusion criteria. Thus, a total of 71 patients were excluded from the study.

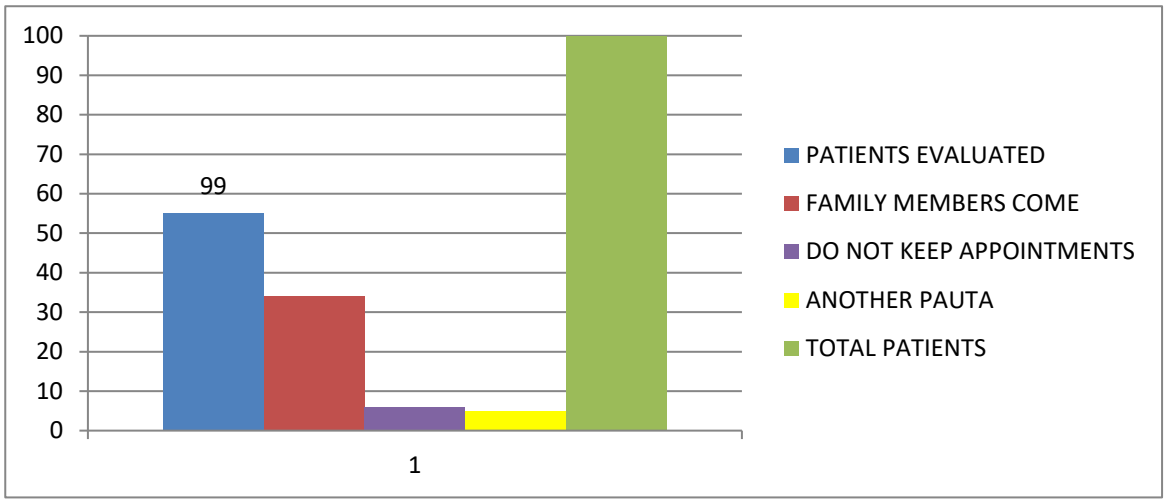

Figure 1. Total number of patients evaluated during the study period.

Concerning the sociodemographic variables age and sex in the 99 patients finally analyzed, Table 1 shows the information.

Table 1. Information on the variables age and sex of the patients in the study.

Age (years)				Male
Media (± Standard deviation)	Median	Fashion	Range (max.-min.)	N (%)
54,3 (± 11,9)	54	68	25-79	50 (50,5)

Variables related to autoimmune disease.

Concerning the variable related to diagnosis, Table 2 shows the distribution of the patients interviewed according to the type of autoimmune disease. It was observed that rheumatoid arthritis was the most frequent pathology in the study, with patients treated with subcutaneously administered biologic drugs.

Table 2. Distribution of patients interviewed.

Variable: Diagnosis	Patients interviewed	
	N	%
Rheumatoid Arthritis	32	32
Psoriasis	27	27
Psoriatic Arthritis	20	20
Ankylosing Spondylitis	12	12
Crohn's disease	8	8
Total	**99**	**100**

Drug-related variables

Concerning the drug, Table 3 shows, in percentage, the use of the biological drugs used by the patients in the study (n=99). It was found that the biological drug most used by the study patients was adalimumab. Secondly, concerning the drug-related regimen, Table 3 shows, in percentage and absolute frequency respectively, the regimen used for the biologic drugs used by the study patients (n=99).

Table 3. Information on drug utilization in the study patients.

Variable: Medication	Patients interviewed	
	N	%
Adalimumab	60	60
Etanercept	14	14
Ustekinumab	12	12
Golimumab	10	10
Tocilizumab	2	2
Abatacept	1	1
Total	**99**	**100**

Table 4 shows that the most frequently used regimen in the study patients is every 2 weeks, logically, because the most prevalent biologic drug is adalimumab, which is usually used every 2 weeks.

Table 4. Information on the variable pattern of drug use in the study patients.

Variable: Guideline	Patients interviewed	
	N	%
2 weeks	43	43
3 weeks	25	25
4 weeks	18	18
Weekly	13	13
Total	**99**	**100**

Table 5 shows the information on the variable hand washing in the version of self-administration of the drug at home, showing whether or not they washed their hands before the administration of the subcutaneous biologic drug, in relation to the patients included in the study (n=99). Most of the patients (49%) did wash their hands before the administration of the subcutaneous biologic drug.

Table 5. Information on the hand washing variable in the version of self-administration of medication at home.

Variable: Hand washing	**Patients interviewed**	
	N	**%**
Yes	89	90
No	10	10
Total	**99**	**100**

Table 6 shows the results on the puncture site variable in the administration of biologic drugs subcutaneously in the study patients. Distribution of the patients in the study according to the puncture site, it should be noted that the puncture site most used by the patients in the study (biologic drugs) was the abdomen since they report that they feel safer self-administering them in this area.

Table 6. puncture site variable

Variable: Puncture site	**Patients interviewed**	
	N	**%**
Abdomen	73	73
Thigh	22	22
Deltoid	4	4
Total	**99**	**100**

The results on the variable rotation of the puncture site in the administration of biologic drugs by subcutaneous route in the patients in the study are shown in Table 7. During the study, through the interview conducted, information was obtained on how many patients had a reaction at the injection site during treatment with subcutaneous administration of biological drugs. This yielded a value of 4 patients, of which 3 patients were treated with Adalimumab and 1 patient with Etanercept.

Table 7. Rotation of the puncture site in the administration of biologic drugs by subcutaneous route.

Variable: Puncture rotation	**Patients interviewed**	
	N	**%**
Yes	81	82
No	18	18
Total	**99**	**100**

The results on the variable reaction at the injection site, how many patients have had this reaction and with which drugs are presented in Table 8. This result was obtained during the interview with the patients, which shows that 2 patients had reactions at the injection site with the biological drug adalimumab, one of them (thigh) stated that he did not rotate the puncture site every time he had to administer the drug because he felt safer administering it at the same puncture site.

Table 8. Drug Injection Site Reaction

Variable: Injection site reaction Medication	**Patients interviewed** (n 99) **Puncture site**	**N**	**%**
Adalimumab	Thigh	2	49.5
Adalimumab	Abdomen	1	25
Etanercept	Abdomen	1	25
Total	**99**	**4**	**99**

Discussion

The findings suggest that the patients with the highest incidence of skin reactions at the injection site were patients administered Adalimumab (3 patients) and Etanercept (1 patient). Clinical studies show that it is necessary to change the puncture site every time the drug has to be administered either from (left-right) or (upper and lower), so there would be no higher frequency of skin reactions at the puncture site such as extravasation, erythema, pruritus (26).

The results of patients treated with adalimumab show a higher rate of skin reactions in 3% of the study population, with a frequent regimen every 2 weeks; it should be emphasized that this drug has this regimen as a usual reference. Previous studies (22) show that this biological drug adalimumab with a higher use presents cutaneous reactions. There are still no published studies on the immunological mechanism of injection site reactions against this drug. Consequently, the results obtained during the study of patients treated with adalimumab (abdomen) are detailed, reporting that they did not wash their hands before administration because the drug itself comes with a wet wipe with alcohol; and for the patient, it was not necessary to do so, and this is one of the main causes involved in skin reactions. Clinical studies show that the World Health Organization (WHO) (33) in 2009 considered that hand hygiene is one of the main measures to reduce diseases (34). The other biologic drug, etanercept, caused injection site reaction in the study patients with 1%. Clinical studies found that injection site reactions in patients with rheumatologic diseases treated with etanercept had a higher incidence of significant puncture site reactions such as

erythema, pruritus and extravasation (26).

The patient treated with etanercept (abdomen) described that he did not know how or why he had presented a skin reaction at the injection site. However, in the clinical study, they found that in injection site reactions, patients with rheumatologic diseases treated with etanercept have a higher incidence of significant injection site reactions such as erythema, pruritus and extravasation. Injection site reactions usually occur within the first month of treatment and typically last 3 to 5 days. Some of the factors that influence the pathology are that there are patients who have an immediate type I hypersensitivity and mediated by Ig; these are receptors of the membrane of mast cells and basophils of peripheral blood which react 15 minutes after the administration of the drug (22).

According to the information obtained from the technical data sheet of the drugs (26), clinical studies report that 12.9% of patients treated with adalimumab develop injection site reactions such as erythema, pruritus, edema, pain and extravasation (26), while etanercept shows that 13.6% of patients treated with this drug present reactions at the injection site. Golimumab, with 5.4% of patients, presented reactions at the injection site after administration of the drug. Next, 10.1% of patients treated with tocilizumab show injection site reactions, while 2.6% of patients treated with abatacept show injection site reactions (26). In the usual clinical practice, it can state that this procedure of home self-administration of the subcutaneous drug nowadays for the health personnel and the patient who uses this treatment, is initially considered an advantage because time and health professionals are optimized. In this study, it was possible to verify that it should be considered to follow up the patients who administer this subcutaneous biological drug since many patients do not perform puncture rotations for fear of misapplying the drug. Home visits should also be made to patients to observe how or by whom the subcutaneous drug is administered. It is interpreted that the greater the use of this drug in patients with this pathology, the more reactions there are at the injection site. To confirm the results, it is necessary to continue the study to know the initial situation, implement improvement strategies and evaluate the achievements obtained in this study. Because of selection bias, due to the inclusion criteria and time limitations for the study, it was not possible to evaluate all the patients (10) who have another regimen (16 weeks). For this reason, the study was only carried out taking as referencing those patients who had a minimum administration frequency of 12 weeks.

Conclusions

Through the interview conducted with the patients in the study, only 4 patients were found to have manifested cutaneous reactions at the injection site out of the 99 patients evaluated; the results are not sufficient to conclude in this regard. Describing the factors that intervene in the reaction at the injection site, it is concluded that not all patients with this subcutaneous biological drug treatment perform rotations at the injection site; it should be emphasized that not all of them do so for fear of misapplying the drug in another puncture site. Another cause that interferes is the puncture site and this depends on the area where it is administered since it is not administered subcutaneously but intradermally or intramuscularly.

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