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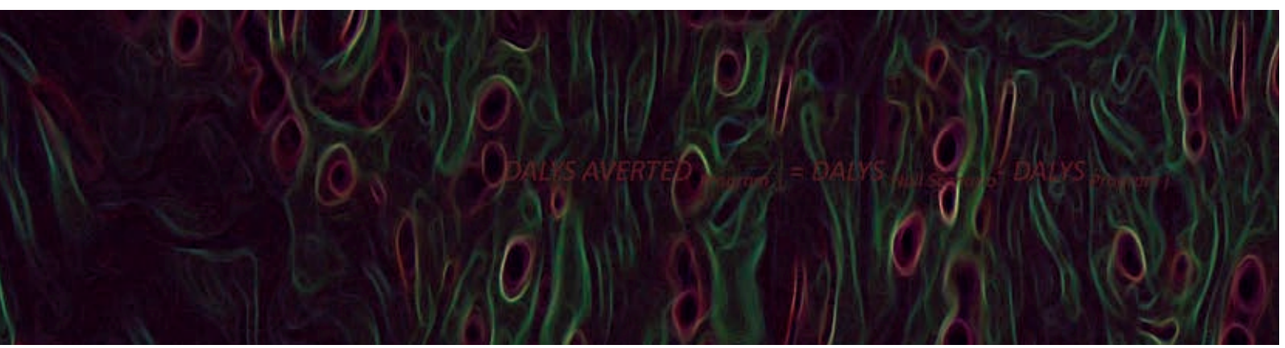

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Photo edited photomicrograph of an infiltrating ductal carcinoma of the breast from the original stained with hematoxylin and eosin, 20X. Courtesy of Haydee Caro Sánchez M.D., Department of Pathology, Instituto Nacional de Cancerología, SS, Mexico. The background equations correspond to some of those described in the article "Estimation of the Cost-Effectiveness of Breast Cancer Screening Using Mammography in Mexico through a Simulation" by Ulloa-Pérez and colleagues, published in this issue of the journal.

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Rev Inves Clin. 2016;68:169-70 RESEARCH LETTER

Classifying Acute Respiratory Distress Syndrome Severity: Correcting the Arterial Oxygen Partial Pressure to Fractional Inspired Oxygen at Altitude

Rogelio Pérez-Padilla, Carmen Margarita Hernández-Cárdenas and Gustavo Lugo-Goytia

Sleep Disorders Clinic, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico

BACKGROUND

In the well-known Berlin definition of acute respiratory distress syndrome (ARDS)[1], there is a recommended adjustment for arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FIO_2) at altitude, but without a reference as to how it was derived. At the same shunt, PaO_2/FIO_2 decreases with altitude[2], impairing a proper comparison of individuals with similar lung damage if they reside at different altitudes and if the shunt is not directly measured, as is the case in most patients. It is then very important in multicenter studies to correct the PaO_2/FIO_2 by altitude or barometric pressure (i.e. raise the value of PaO_2/FIO_2 obtained at altitude), but unfortunately, the adjustment is not a simple function of altitude or barometric pressure[2]. The correction suggested by the working group does the opposite of what is needed because it requests a multiplication by a fraction: barometric pressure (Pbar)/760. If, instead of multiplying by Pbar/760, we divide by the ratio (to set, for example, varying limits for ARDS severity at different altitudes), the resulting PaO_2/FIO_2 is closer to that expected at sea level for lower shunts (and high PaO_2/FIO_2), but overcorrects at higher shunts and of course does not take into account changes in PaO_2/FIO_2 due to modifications of FIO_2[3]. Our aim was to develop an equation able to take into account the impact of altitude on PaO_2/FIO_2 so that patients from different altitudes could be compared at a more homogeneous degree of lung damage.

METHODS

Computational lung models of gas exchange provide a better understanding of the problem. We performed a computer simulation changing FIO_2 from 0.21 to 1.0, altitude from sea level to 3,000 m, barometric pressure from 537 to 760 mmHg, and shunt from 5 to 50% of cardiac output, maintaining constant hemoglobin, carboxyhemoglobin, p50, 2,3-diphosphoglycerate (2-3DPG), cardiac output, and acid-base status and without incorporating into the model ventilation/perfusion (V/Q) inequalities[4]. Calculated values at varying altitudes were incorporated into a database

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Table 1. Classification of acute respiratory distress syndrome severity in 173 patients admitted to the intensive care unit at an altitude of 2,240 m

ARDS severity by level of PaO_2/FIO_2	Without adjustment n (%)	With the Berlin definition adjustment n (%)	With suggested adjustment (lung models) n (%)
Mild	34 (19.7)	8 (4.6)	71 (41.0)
Moderate	104 (60.1)	97 (56.1)	97 (56.1)
Severe	35 (20.2)	68 (39.3)	5 (2.9)

ARDS: acute respiratory distress syndrome; PaO_2/FIO_2 arterial oxygen partial pressure to fractional inspired oxygen.

and then simpler linear multiple regression equations of sea level-adjusted PaO_2/FIO_2 were obtained as a function of FIO_2, altitude above sea level (or barometric pressure), and measured PaO_2/FIO_2, all with an $R^2 > 0.99$. The impact of the proposed adjustment on the severity of ARDS classification was tested on a group of patients with ARDS secondary to pneumonia admitted during 2014-2015 to the intensive care unit of a referral center for respiratory diseases in the metropolitan area of Mexico City (altitude 2,240 m above sea level).

RESULTS

Using altitude in meters to estimate PaO_2/FIO_2 at sea level (PaO_2/FIO_2SL):

$$PaO_2/FIO_2SL = (PaO_2/FIO_2 * 1.245) + (FIO_2 * 51.51) + (0.0307 * altitude) - 88$$

Using mean Pbar in mmHg:

$$PaO_2/FIO_2SL = 224.46 + (PaO_2/FIO_2 * 1.245) - (Pbar * 0.413389) + (FIO_2 * 51.55)$$

Table 1 shows the severity of ARDS with the original classification and after the proposed adjustment, duplicating the percentage of patients with mild ARDS.

DISCUSSION

These proposed adjustments appropriately raise the PaO_2/FIO_2 measured at altitude, so that the same sea level cut-point limits to classify ARDS severity can be utilized when comparing patients living at different altitudes above sea level. Empirical testing of estimations is necessary although rather complicated because several factors that are maintained constant in the computer simulation regularly have variations in critical patients.

The adjustments are important as is evidenced by the shift in severity classification of a group of patients with ARDS (Table 1), displaced towards milder stages, as expected, because part of the decreased PaO_2/FIO_2 observed in Mexico City was due to altitude and not to lung damage. Classifications by saturation of oxygen (SaO_2/FIO_2, not shown) had a similar tendency.

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Rev Inves Clin. 2016;68:171-5 BRIEF COMMUNICATION

Expression of HER2/Neu in B-Cell Acute Lymphoblastic Leukemia

Sergio Rodriguez-Rodriguez[1,2], Alan Pomerantz[1,2], Roberta Demichelis-Gomez[1], Georgina Barrera-Lumbreras[1], Olga Barrales-Benitez[1] and Alvaro Aguayo-Gonzalez[1]*

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ABSTRACT

Background: The expression of HER2/neu in B-cell acute lymphoblastic leukemia has been reported in previous studies. **Objective:** The objective of this research was to study the expression of HER2/neu on the blasts of patients with acute leukemia from the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran. **Methods:** From June 2015 to February 2016, a HER2/neu monoclonal antibody was added to the panel of antibodies that we routinely use in patients with acute leukemia. An expression of ≥ 30% was considered positive. **Results:** We studied 33 patients: 19 had *de novo* leukemia (57.6%), three (9.1%) were in relapse, and in 11 (33.3%) their status could not be specified. Seventeen patients (51.5%) were classified as B-cell acute lymphoblastic leukemia with a median expression of HER2/neu of 0.3% (range 0-90.2). Three patients with B-cell acute lymphoblastic leukemia were positive for HER2/neu: 89.4%, 90.9%, and 62.4%. The first and third patient had *de novo* B-cell acute lymphoblastic leukemia. The second patient was in second relapse after allogeneic stem cell transplant. All three patients were categorized as high-risk at the time of diagnosis. **Conclusions:** In the studied Mexican population, we found a positive expression of HER2/neu in 17% of the B-cell acute lymphoblastic leukemia patients, similar to previous studies in which the expression was found in 15-50%. (REV INVES CLIN. 2016;68:171-5)

Key words: Acute leukemia. Acute lymphoblastic leukemia. HER2/neu. Trastuzumab. Monoclonal antibody.

INTRODUCTION

Human epidermal growth factor 2 (HER2/neu) is a transmembrane tyrosine kinase receptor that belongs to the ErbB family[1]. Overexpression of HER2/neu has been found in 15-25% of patients with breast cancer, as well as in other carcinomas (i.e. stomach, colon, ovary, lung and cervix)[2-4]. In breast cancer, its presence has been correlated with a worse outcome (i.e. shorter survival time or lower response to chemotherapy)[5,6]. The use of trastuzumab, a humanized 4d5 monoclonal antibody that interferes with the HER2/neu receptor, in combination with chemotherapy has improved the overall response and survival in patients with breast cancer[7-10].

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In 1995, Bühring, et al. reported for the first time the presence of HER2/neu on leukemic blasts of the B-lymphocytic lineage[11]. Researchers analyzed the blasts of 18 pediatric and 86 adult patients with chronic or acute leukemia and found the presence of HER2/neu in 47.6% (n = 10/21) of the adult patients with B-cell acute lymphoblastic leukemia (ALL) and 13.3% (n = 2/15) of the pediatric patients with B-cell ALL. Additionally, 75% (n = 3/4) of patients with chronic myeloid leukemia in B-lymphoid blast crisis expressed high levels of HER2/neu. No expression was found on the blast cells of patients with T-cell ALL, acute myeloid leukemia (AML), or chronic lymphocytic leukemia. After these results were published, other authors have corroborated the presence of HER2/neu on blast cells of pediatric and adult patients with B-cell ALL[12-16]. The purpose of this study was to demonstrate the presence of HER2/neu on the blast cells of adult Mexican patients with acute leukemia (AL) from the Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran.

MATERIALS AND METHODS

Study design

We included all the patients that according to the immunophenotypic analysis were diagnosed with AL (whether they had *de novo* or relapse AL) in our institution between June 2015 and February 2016. Anti-HER-2/neu (Neu 24.7/phycoerythrin) (Beckton Dickinson, San José, CA, USA) monoclonal antibodies were added to the panel of antibodies that are routinely used in patients with AL in the Hematology and Oncology Department.

Flow cytometry

An eight-color flow cytometry panel was used, which included the following fluorochromes: phycoerythrin (PE), fluorescein isothiocyanate (FITC), peridinin chlorophyll (PerCP), allophycocyanin (APC), V450, V500, PE and cyanine die 7 (PE-Cy7), and PerCP-Cy5.5. The panel of antibodies included were: HER2/neu PE, CD2-FITC, cytoplasmic CD3 (cCD3-FITC), CD5-PE, CD7-APC, CD10-PE or CD10-APC, CD11b-Cy5, CD13-PE, CD14-PE, CD15-FITC, CD19-FICT, CD20-FITC or CD20-V450, CD22-PE or CD22-APC, CD33-PE or CD33-APC, CD34-PE, CD41-PE, CD56-FITC, CD61-FITC, CD64-PE or CD64-APC, cCD79a-PE, CD117-APC, CD235a-FITC, anti-MPO-FITC, HLA-DR-V450, IgM-PE or IgM-APC. Data were obtained and analyzed in a FACSCanto™ II flow cytometer (Becton Dickinson Immunocytometry Systems, San José, CA, USA) with the aid of FACSDiva™ software (Becton Dickinson, San José, CA, USA). Samples were analyzed via a CD45 gating technique, which allowed the laboratory to analyze only the blast population. Positive expression was considered when a marker was present in 10% or more of the blast population in cytoplasmic markers (cCD3, cCD79a, cIgM, and MPO) and CD34, 20% or more in myeloid markers and HLA-DR, and 30% or more in lymphoid markers and HER2/neu.

RESULTS

Patients

The HER2/neu antibody had a median expression of 0.3% (range 0-90.2). The median age of the patients was 41 years (17-80), and 17 patients were male (51.5%). Nineteen patients had *de novo* leukemia (57.6%), three (9.1%) were in relapse, and in 11 patients (33.3%) the relapsed or *de novo* status was not specified due to the fact that they had not been followed-up at our institution. Seventeen patients (51.5%) were diagnosed with B-cell ALL, one (3%) with T-cell ALL, 13 (39.4%) with AML, and two (6.1%) with acute leukemia of ambiguous lineage. Of the 17 B-cell ALL patients, four (23.5%) were sub-classified as pro-B cell ALL, 11 (64.7%) as common B-cell ALL, and two (11.8%) as pre-B cell ALL.

HER2/neu expression

HER2/neu was not expressed on the blast population of the patients with AML, T-cell ALL, or acute leukemia of ambiguous lineage. Among the 17 patients with B-cell ALL, the median expression of HER2/neu was 0.3% (0-90.2) and three patients (3/17, 17.6%) were positive for HER2/neu. The demographic and clinical characteristics of the patients with B-cell ALL are shown in table 1.

Patient 1 had *de novo* leukemia and was classified as a high-risk individual due to the presence of the

Table 1. Demographic and clinical characteristics of patients with B-cell acute lymphoblastic leukemia

	HER2/neu+ (n = 3)	HER2/neu– (n = 14)
Gender, no. patients (%)		
Male	2 (66.7)	6 (42.9)
Female	1 (33.3)	8 (57.1)
Age, years (range)	26 (22-44)	34 (17-65)
Immunophenotype, no. patients (%)	2 (66.7)	8 (57.1)
De novo	1 (33.3)	1 (7.1)
Relapse	–	5 (35.7)
Not specified		
Immunological subtype, no. patients (%)		
Pro-B (I)	–	4 (28.6)
Common B-cell (II)	3 (100)	8 (57.1)
Pre-B (III)	–	2 (14.3)
Mature B-cell (IV)	–	–
Sample origin, no. patients (%)		
PB	2 (66.7)	5 (35.7)
BM	1 (33.3)	7 (50.0)
Not specified	–	2 (14.3)
Blasts in PB or BM, % (range)	77.4 (61- 87)	66.6 (3.0-90.6)
Marker expression, % (range)		
HER2/neu	89.4 (62.4-90.2)	0.15 (0-6.6)
CD34	99.4 (25.6-99.6)	94.5 (0.1-99.8)
CD10	66.4 (61.9-72)	69.8 (1.0-99.5)
CD19	95.3 (42.9-99.8)	97.8 (94.2-98.5)
CD20	13 (4.3-18.3)	5.7 (0.2-97.6)
CD22	85.6 (76.1-98.0)	92.3 (0.8-99.0)

ALL: acute lymphoblastic leukemia; PB: peripheral blood; BM: bone marrow.

Philadelphia chromosome and a high white blood cell count at diagnosis; HER2/neu expression on the blast population of the patient was 89.4%. Patient 2 was in second relapse after allogeneic stem cell transplant, and was classified as high-risk due to the presence of a high white blood cell count at diagnosis; HER2/neu expression on the blast population in this patient was 90.2%. Patient 3 had *de novo* leukemia, and was classified as high-risk due to a high white blood cell count at diagnosis; HER2/neu expression on the patient's blast cells was 62.4%.

Expression of other markers

Patients 1 and 2 expressed CD34, CD19, and CD22 on > 90% of the blast population. CD10 was expressed on > 70% of the blast population in patient 1, while patient 2 expressed CD10 on > 60% of the blasts. Patient 3 expressed CD19 on > 90% of the blast population, CD22 on > 70% of the blast population, CD10 on > 60% of the blast population, and CD34 on > 20% of the blasts. Additionally, this patient was the only one that expressed CD20.

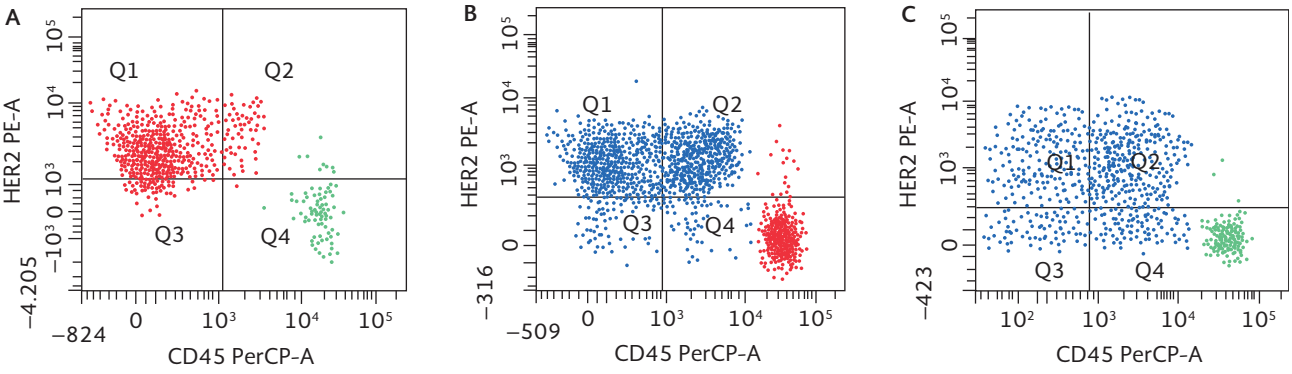
Outcome of patients

Patient 1 achieved complete remission after treatment with a hyper-cyclophosphamide, vincristine, doxorubicin (also known by its trade name, Adriamycin), and dexamethasone (CVAD) regimen. When we were writing this report, patient 2 was starting treatment with a modified hyper-CVAD regimen that included trastuzumab and excluded doxorubicin (the patient was in a dire state and, due to the cardiotoxicity of both trastuzumab and anthracyclines, we decided to exclude doxorubicin). Patient 3 achieved complete remission after treatment with hyper-CVAD and rituximab.

DISCUSSION

In previous studies, HER2/neu was positive in 15-50% of the patients with B-cell ALL[11-16]. Our results confirm the existence of HER2/neu in AL of a B-lymphoblastic lineage, and that the percentage of patients with B-cell ALL positive for HER2/neu in our population (17.6%)

Figure 1. Flow cytometry dot plots representing HER2/neu expression in B-cell acute lymphoblastic leukemia blasts. **A.** Patient 1 with 87% of blasts (red dots); 89.4% of the blasts expressed HER2/neu and 4.5% co-expressed HER2/neu and CD45. **B.** Patient 2 with 61% of blasts (blue dots); 90.9% of the blasts expressed HER2/neu and 47.5% co-expressed HER2/neu and CD45. **C.** Patient 3 with 76.4% of blasts (blue dots); 62.4% of the blasts expressed HER2/neu.



falls within the range reported by other authors. Furthermore, the expression of HER2/neu on the blast population of these patients (60-90%) was similar to that found by previous authors[13,14] (Fig. 1).

As mentioned before, the expression of HER2/neu in breast cancer is usually associated with a poor prognosis[5,6]. Some authors have stated that the expression of HER2/neu on the blasts of patients with B-cell ALL may also be associated with a poor outcome[12,13,15]. However, Haen, et al. stated that, since the patients were followed for a short period of time, these studies were underpowered to determine a valid prognostic significance[16]. In their study, which gathered information in a retrospective manner from patients that were followed-up to 15 years, they found no negative correlation between HER2/neu expression and chemoresistance, relapse rates, disease-free survival, or overall survival[16].

Furthermore, the antitumor activity of HER2/neu monoclonal antibodies was evaluated in three studies[12,15,16]. In two of these studies, the researchers demonstrated, *in vitro,* the lysis of blasts from patients with HER2/neu-positive B-cell ALL when exposed to an anti-HER2/neu antibody and either cytotoxic T-lymphocytes or NK cells[12,16]. To this day, only one study has used trastuzumab *in vivo* in patients with HER2/neu-positive B-cell ALL. The study included 15 adult patients with relapsed or refractory disease that received trastuzumab as their single treatment, and an overall response rate of 13% was achieved[15].

From the low overall response rate reported in the study that used trastuzumab in patients with HER2/neu-positive B-cell AL, it could be assumed that trastuzumab has no use in the treatment of these patients. However, in breast cancer, the use of trastuzumab as a single agent provides similar overall responses (15-26%)[17,18]. Consequently, we believe that in patients with HER2/neu-positive B-cell ALL, the rate of response to trastuzumab should be evaluated alongside other chemotherapeutic regimens.

Another factor that could impact the treatment strategies in these patients is the expression of other markers besides HER2/neu. A frequent association of HER2/neu with CD20 and CD34 has been observed[14]. In our study, we found that the markers more frequently expressed besides HER2/neu were CD19 and CD22. Therefore, in HER2/neu-positive B-cell ALL patients, trastuzumab and the usual chemotherapeutic regimens could be used in combination with other biological therapies (e.g. the anti-CD22 monoclonal antibody epratuzumab) in an attempt to improve the overall responses of these individuals[19].

Despite the relatively small number of samples, we proved the existence of HER2/neu in Mexican patients with B-cell ALL. Thus, we will continue to search for the expression of HER2/neu in patients with B-cell ALL to assess the clinical impact of this peculiar phenomenon. Additionally, we are planning to continue

the evaluation of trastuzumab in combination with other anticancer treatments in patients who present HER2/neu-positive B-cell ALL.

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Rev Inves Clin. 2016;68:176-80 BRIEF COMMUNICATION

Impact of a Movement Disorders Clinic on the trends of Parkinson's Disease Consultations at a Tertiary Referral Center

Teresa Corona[1], Amin Cervantes-Arriaga[1], Leora Velásquez-Pérez[2] and Mayela Rodríguez-Violante[1,3*]

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ABSTRACT

Background: Outpatient clinics for movement disorders provide specialized diagnosis and treatment services for the specific needs of this patient population. **Objective:** Describe the impact of implementing a Movement Disorder Clinic on the trends of consultations per year and hospitalizations of subjects with Parkinson's disease at a tertiary referral center. **Methods:** A retrospective study was carried out. We collected data from the Clinical File Archive and the Epidemiology Department at the National Institute of Neurology and Neurosurgery in Mexico. Data from January 1, 1999 through December 31, 2015 were included for analysis. **Results:** The number of total consultations had an increase of 632.1% between 1999 and 2015. Follow-up visits represented up to 95% of the consultations. Peaks found correlated with the inclusion of new specialists in the clinic. Regarding hospitalization, the number of patients discharged with a diagnosis of Parkinson's disease increased from a median of 17 (range 9-35) to 46 patients (range 31-53) per year. **Conclusions:** The implementation of a multidisciplinary Movement Disorders Outpatient Clinic in a tertiary referral center had a direct impact on the total number of consultations per year, mainly follow-up visits. The latter may reflect in an improvement in the quality of care. (REV INVES CLIN. 2016;68:176-80)

Key words: Movement disorders. Outpatient clinic. Parkinson's disease.

INTRODUCTION

The main objective of a specialized outpatient clinic is to provide patients with expedited access to diagnosis, treatment and, when needed, fast reference to other specialists. The implementation of a specialized clinic should optimize the time and quality of care.

Outpatient clinics for movement disorders began to develop in the early 1990s[1] and had their peak during the 2000s.

The role of a movement disorder clinic has been highlighted as a consequence of the need for a multidisciplinary approach. In addition to neurologists with

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expertise in the field, a movement disorder clinic requires other specialists and health-related professionals such as speech therapists, physical rehabilitation therapists, nursing specialists, neuropsychologists, and neuropsychiatrists. It has also been suggested that the inclusion of a pharmacist in the clinic's team is of great value[2]. Moreover, specific activities such as clinical and motor video recording are usually required[3].

It has been reported that quality of life of subjects with Parkinson's disease (PD) improves in up to 30% when attention is given in a movement disorder clinic in comparison to a general outpatient clinic[4]. Another study proved that, in addition to the symptomatic benefit, subjects with PD reduced health-related indirect costs after being referred to a movement disorder clinic[5].

Since 2009, the US National Parkinson Foundation has had a certification program of Centers of Excellence for the specific case of PD. This certification requires that the movement disorder clinic meets the following criteria:

– Sufficient volume of patients to ensure exposure to various manifestations of the disease as well as a wide range of therapeutic options;

– Provides care based on a model of a multidisciplinary team;

– Has a team of neurologists with formal training in movement disorders that balance clinical practice with academic and research activities;

– A spectrum of therapeutic options, including an experienced team of neurosurgeons;

– Demonstrates commitment to education and clinical training;

– Promotes and encourages programs of physical activity and nutrition;

– Provides current information to families and caregivers;

– Participates in the development of new knowledge through collaborative research and own research;

– Provides access to experimental therapies through the conduct of clinical trials.

To date there are 31 certified centers in the USA, one in Australia, eight in Canada, one in Germany, one in Israel, one in the Netherlands, one in Singapore, one in Taiwan, and two in the UK. There is no certified center in Latin America, although recently a center in the Bahamas has been certified. In general, the time from the implementation of an movement disorder clinic until its certification is estimated to be 10 years.

The objective of this brief communication is to describe the impact of implementing an movement disorder clinic on the number of consultations of subjects with PD per year given at the outpatient clinic, as well as on the number of hospitalizations, at the National Institute of Neurology and Neurosurgery.

MATERIALS AND METHODS

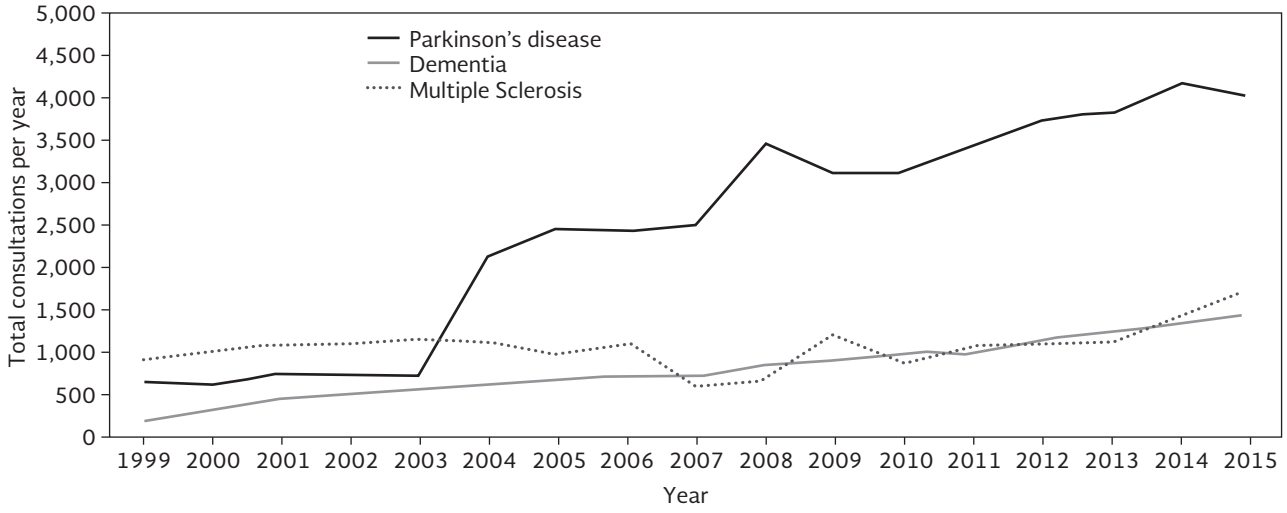
We collected data from the Clinical File Archive and the Epidemiology Department of the National Institute of Neurology and Neurosurgery of Mexico from January 1, 1999 through December 31, 2015. Data included the total number of first-time consultations (new cases), total number of follow-up consultations, and total number of hospitalizations due to PD. For this study, subjects with PD were identified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code G20. In addition, data from two other specialized clinics were extracted for comparison. Data for dementia consultations (ICD-10 code G30) at the Cognition Clinic and data for multiple sclerosis consultations (ICD-10 code G35) at the Multiple Sclerosis Clinic were obtained using the same methodology.

A waiver of informed consent was approved by the Ethics Committee due to the retrospective nature of the study and the fact that no identifying information was used. The study was approved by the Institutional Review Board.

Statistical analysis

Descriptive statistics was carried out using measures of central tendency and dispersion. Demographic and other qualitative data were expressed in terms of

Figure 1. Number of Parkinson's disease, dementia, and multiple sclerosis first and follow-up consultations per year for the period 1999 to 2015.



means and standard deviations. When data did not fit normal distribution, median and ranges were used. Qualitative data were expressed in terms of frequencies and percentages.

RESULTS

Between 1999 and 2015 a total of 41,926 consultations were given at the Movement Disorder Outpatient Clinic. Specifically, PD (G20) was among the first 10 causes of consultation at the National Institute of Neurology and Neurosurgery in all years, usually being the third or fourth overall cause of first-time consultation at the outpatient clinic. In 2014 PD was the third cause of consultation, and in 2015 it was the second overall cause of consultation at the outpatient clinic of the Institute.

The total number of consultations increased by 632.1% between 1999 and 2015. Figure 1 shows the total number of consultations given at the Movement Disorders Clinic, Cognition Clinic, and Multiple Sclerosis Clinic per year. Regarding PD consultations, two major peaks can be identified, the first one in 2004 and the second one in 2008. When analyzing only the first-time visits, a total of 85 first-time consultations were given in 1999 compared to a total of 225 in 2015. To be highlighted is the fact that first-time consultations showed a sudden drop from 2003 to 2004 in relation to follow-up visits (23.8-6.4 vs. 76.2-93.6%). The first-time visits in the following years ranged between 4.0 and 6.6%.

In comparison, a total of 199 consultations were given at the Cognition Clinic in 1999, increasing to 1,470 in 2015. Similarly, multiple sclerosis consultations at the outpatient clinic increased from 925 to 1,717 in the same timeframe.

Regarding hospitalization, the number of patients discharged with a diagnosis of PD has also increased in the last six years. During the period between 2001 and 2008 the median of patients hospitalized per year with a diagnosis of a PD was 17 (range 9-35), while between 2009 and 2015 the median increased to 46 patients (range 31-53) per year. The main reasons for hospitalization were diagnostic work-up, acute levodopa challenge, or undergoing deep brain stimulation (DBS) surgery. In regards to DBS surgery, the number of procedures ranged between 10 and 15 per year from 2008 to date. Detailed information on the number of consultations is shown in table 1.

DISCUSSION

The Movement Disorders Outpatient Clinic of the National Institute of Neurology and Neurosurgery in Mexico City was established in 1999, but it was not

Table 1. Frequency of Parkinson's disease consultations from 1999 to 2015 including first-time consultations, follow-up consultations, and hospitalizations

Year	Total consultations	Yearly percentage change	First-time consultations	Follow-up consultations	Overall cause of consultation	Number of hospitalizations
1999	634	–	85 (13.4%)	549 (86.6%)	3rd	NA
2000	626	–1.3%	132 (21.0%)	494 (79.0%)	5th	NA
2001	745	+19.0%	152 (20.4%)	593 (79.6%)	5th	17
2002	734	–1.5%	142 (19.3%)	592 (80.7%)	5th	16
2003	743	+1.2%	177 (23.8%)	566 (76.2%)	4th	35
2004*	2,137	+187.0%	137 (6.4%)	2,000 (93.6%)	4th	9
2005	2,461	+15.2%	162 (6.6%)	2,299 (93.4%)	4th	17
2006	2,448	–0.5%	137 (5.6%)	2,311 (94.4%)	4th	24
2007	2,501	+1.6%	140 (5.6%)	2,361 (94.4%)	5th	27
2008†	3,484	+39.3%	134 (3.8%)	3,350 (96.2%)	4th	15
2009	3,109	–10.8%	206 (6.6%)	2,903 (93.4%)	4th	46
2010	3,136	+0.9%	163 (5.2%)	2,973 (94.8%)	4th	53
2011	3,430	+9.4%	146 (4.3%)	3,284 (95.7%)	5th	52
2012	3,736	+8.9%	148 (4.0%)	3,588 (96.0%)	5th	50
2013‡	3,823	+2.3%	180 (4.7%)	3,643 (95.3%)	4th	31
2014	4,171	+9.1%	184 (4.4%)	3,987 (95.6%)	3rd	41
2015	4,008	–3.9%	225 (5.6%)	3,783 (94.4%)	2nd	43

*First movement disorder specialist in hospital staff. †First movement disorder specialist in hospital staff. ‡Third movement disorder specialist in hospital staff. NA: Not available.

until 2004 that the first movement disorder specialist was included. The Movement Disorders Clinic is currently based on a model of a multidisciplinary team, which includes board-certified neurologists with formal training who work closely with functional neurosurgeons, neuropsychiatrists, neuropsychologists, physical therapists, language therapists, and geneticists. In addition, the clinic works closely with specific family and patient support groups within the institute, as well as with external groups such as the Mexican Association of Patients with Parkinson. The Institute is currently the only hospital with a movement disorder teaching program (High Specialty Course in Parkinson's Disease and Movement Disorders) recognized by the National Autonomous University of Mexico. This one-year fellowship has also been recognition by the Pan American Section of the International Parkinson and Movement Disorder Society (http://www.movementdisorders.org/MDS/Regional-Sections/Pan-American-Section/PAS-Fellowship-Programs/Mexico.htm). Both, investigator-initiated research and protocols sponsored by the pharmaceutical industry are regularly carried out.

Nevertheless, according to the National Parkinson Foundation, the first requirement for achieving excellence is a sufficient volume of patients to ensure exposure to various manifestations of the disease, as well as a wide range of therapeutic options. In this matter, our Movement Disorder Clinic provided approximately 4,000 consultations in the last three years. Most of these consultations were follow-up visits that allow for improved care of the patient with PD. Interestingly, the ratio of first-time/follow-up visits has remained steady for the last 10 years, resulting in almost 95% of the consultations being follow-up visits and only around 5% being first-time cases. This may be interpreted as a reflection of the referral rate to a tertiary center in Mexico.

The Movement Disorders Clinic at our Institute properly began in 1999, but it was not until 2004 that the first movement disorder specialist was included. The number of consultations had a threefold increase from 2003 to 2004. The second movement disorder specialist was hired in 2008, and an additional 40% increase on the number of consultations was seen. It should be pointed out that a third movement disorder specialist was included on the staff in 2013 with a lesser impact on the number of consultations, probably as a consequence of appointment scheduling constraints.

In comparison, data from the Cognition Clinic shows a slower but steady increase on the number of consultations. This can be partially explained by the fact that this clinic has currently only one specialist; in addition, the lack of a highly effective treatment may also result in a higher risk of loss at follow-up[6].

Conversely, the number of consultations in the Multiple Sclerosis Clinic appears to be less predictable. It should be noted that this clinic was established almost at the same time and has the same number of specialists as the Movement Disorders Clinic. In this case, the development of effective disease-modifying therapies may have had an impact on the number of required consultations per year. Finally, patients who experience a relapse attend the emergency department rather than the outpatient clinic[7].

On the other hand, the increase in the number of subjects with PD who are hospitalized again is associated with the inclusion of specialized neurologists, but also with an increasing number of DBS surgeries performed at the Institute. A complete and reliable registry of patients who underwent DBS surgery has been available since 2008 when the Local Committee for Movement Disorder Surgery was established. This committee evaluates the appropriateness of candidates for DBS based also in a multidisciplinary approach.

This study has limitations. First, demographic data are limited. Data such as age, gender, and disease duration will be of great interest, but are currently unavailable. Second, since the data were extracted from an existing database, the possibility of misdiagnosis cannot be properly assessed. Nevertheless, the misdiagnosis rate is expected to be low as a consequence of it being a specialist clinic. Third, our study is subject to a referral bias. Data from a tertiary healthcare center with a specialized Movement Disorders Clinic, as such, may not reflect the same population trends seen in most primary contact centers or by the general practitioner. For example, essential tremor is considered the most common adult movement disorder worldwide[8], but at our Movement Disorders Clinic, the main cause of consultation is PD.

In conclusion, the implementation of a Movement Disorders Clinic with a multidisciplinary approach has had a direct impact on the number of consultations per year, mainly follow-up visits, in a tertiary referral center. Further studies assessing the effect of this specialized clinic on patient-centered outcomes, such as health-related quality of life, are still needed.

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PERMANYER

Rev Inves Clin. 2016;68:181-3 BRIEF COMMUNICATION

Mexican Biosimilar Filgrastim for Autologous Hematopoietic Stem Cell Mobilization and Transplantation

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ABSTRACT

Background: Following the release of the initial presentation of filgrastim (granulocyte colony-stimulating factor), several biosimilars have been developed worldwide. **Objective**: To study the efficacy of a Mexican biosimilar granulocyte colony-stimulating factor in a single transplant center. **Methods**: In a group of 19 consecutive patients with multiple sclerosis given autografts, we employed granulocyte colony-stimulating factors to mobilize stem cells from the bone marrow to the peripheral blood, either the original granulocyte colony-stimulating factor (n = 10) or a Mexican granulocyte colony-stimulating factor biosimilar (n = 9). **Results**: The efficacy of both agents was similar in mobilization capacity, white blood cell count rise, stem cell collection, and kinetics of auto-engraftment. **Conclusion**: We conclude that both granulocyte colony-stimulating factor agents were similar in their efficacy to mobilize stem cells and usefulness in autografts. (REV INVES CLIN. 2016;68:181-3)

Key words: Biosimilar, Filgrastim. G-CSF. HSCT.

INTRODUCTION

The human recombinant granulocyte colony-stimulating factor (G-CSF) filgrastim has been used in the mobilization and transplantation of $CD34^+$ peripheral blood hematopoietic stem cells (PBHSC) as well as in the prophylaxis of chemotherapy induced neutropenia. The first G-CSF employed in clinical practice was Neupogen® (Amgen, Thousand Oaks, CA, USA); however, the introduction of generics and biosimilars later on has resulted in saving the world's healthcare budget an enormous amount of money[1].

Recently, a biosimilar filgrastim agent has been developed, produced, and used in Mexico (Filatil®, Probiomed, Atzcapotzalco, Mexico). To assess its efficacy, we conducted an observational, randomized, prospective, longitudinal study in a single center in Mexico in patients with multiple sclerosis (MS) to assess the efficacy and safety of two G-CSF agents, the original

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Table 1. Arithmetic mean (range) of the variables analyzed in the patients given granulocyte colony-stimulating factor agents (Neupogen® or Filatil®)

	Neupogen®	Filatil®	p value
Number of patients	10	9	
Total WBC after mobilization and before apheresis, × 10^9/l	17 (2-39)	23 (1-45)	0.41
Granulocyte count before apheresis, × 10^9/l	14 (1-31)	18 (0.5-40)	0.39
Number of apheresis needed to obtain > 1 × 10^6/kg $CD34^+$ PBHSC	1 (1-2)	1 (1-2)	0.66
Number of $CD34^+$ PBHSC obtained per apheresis, × 10^6/kg	2 (1-10)	2 (1-4)	0.29
Number of $CD34^+$ PBHSC grafted, × 10^6/kg	3 (1-10)	2 (1-6)	0.16
Days to recover above 0.5 × 10^9/l granulocytes	9 (6-12)	10 (8-11)	0.97

All the differences are statistically non-significant employing Fisher´s exact test.
PBHSC: peripheral blood hematopoietic stem cells; WBC: white blood cell.

G-CSF and the Mexican biosimilar G-CSF, in both the mobilization and transplantation of $CD34^+$ PBHSC.

METHODS

The PBHSC mobilization schedule was done with cyclophosphamide (Cy) and filgrastim (G-CSF). Intravenous Cy (50 mg/kg) was delivered in a 120-minute period on days −11 and −10. Subcutaneous G-CSF (10 µg/kg twice daily) was delivered on days −9 to −1. Apheresis was performed on day − 2 to obtain at least 1 x 10^6 viable $CD34^+$ cells/kg. As conditioning, intravenous Cy (50 mg/kg) was delivered on days −2 and −1 followed by MESNA, ondansetron, dexamethasone and pantoprazole. G-CSF 5 µg/kg once daily was re-started on day +3 until granulocyte recovery was above 0.5 x 10^9/l.

RESULTS

Nineteen consecutive patients with MS (12 females) with a median age of 47 years (30-65) were prospectively randomized to be given G-CSF, either the original G-CSF (n = 10), or the Mexican biosimilar. At the end of the deployment, the total white blood cell count (WBC) as well as the absolute granulocyte count was similar for the two groups of patients. The number of aphereses needed to obtain at least 1 x 10^6 viable $CD34^+$ cells/kg, as well as the number of $CD34^+$ PBHSC obtained in each apheresis, was similar for patients given either G-CSF. The time to recover above 0.5 x 10^9/l granulocytes was also similar for both G-CSF agents. Bone pain presented in four patients in the original G-CSF group and in three in the biosimilar group. Table 1 summarizes these results; the differences observed were statistically non-significant employing Fisher´s exact test.

DISCUSSION

In patients with hematological malignancies, comparisons of efficacy between different G-CSF agents are difficult since many variables may introduce bias, such as the underlying disease and hence the type and amount of chemotherapy previously delivered to the patients[2-4]. In this group of MS patients, there was no history of previous exposure to chemotherapy and the comparisons may be more valid, despite the low number of individuals studied[5]. In this study, we found no differences in efficacy between the original G-CSF and the Mexican biosimilar; these results support the idea that the two G-CSF agents are equally effective in mobilizing and autografting $CD34^+$ PBHSC. Along this line, Danylesko, et al.[2] have shown the usefulness of a biosimilar human G-CSF made in Israel (Tevagrastim®), whereas Nahon, et al.[3] employed Zarzio®, another biosimilar G-CSF made in France, and both agents were found to be equally effective compared to Neupogen®. In a different study published by Sivgin, et al.[6], the biosimilar Leucostim® induced a significantly higher count of peripheral blood $CD34^+$ compared with the Neupogen® group. The efficacy of biosimilar G-CSF versus Neupogen® in multiple studies worldwide has proven to be equivalent and to provide a cost-effective strategy in all instances[7-11].

The information obtained from this study should be added to that coming from other trials concerning the usefulness of G-CSF biosimilars worldwide.

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PERMANYER

Rev Inves Clin. 2016;68:184-92 ORIGINAL ARTICLE

Estimation of the Cost-Effectiveness of Breast Cancer Screening Using Mammography in Mexico Through a Simulation

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ABSTRACT

Background: Currently, breast cancer is the most prevalent tumor among Mexican women. Screening methods such as mammography could potentially reduce the health and economic burden of breast cancer; however, its risk-benefit balance is still unclear. **Objective:** To estimate the cost-effectiveness of different breast cancer screening programs using mammography in Mexico and to contribute to the decision-making process on this preventive measure. **Methods:** A simulation study was performed using population data and incidence rates. Several screening programs were assessed using the cost-effectiveness methodology recommended by the World Health Organization. **Results:** The feasible recommended screening program has an examination schedule periodicity of every three years, with a population coverage of 0, 15, 18, 20, 25, 20, 18, and 0% for the age groups of 25-40, 40-45, 45-50, 50-55, 55-60, 60-65, 65-70, and 70-75 years, respectively. **Conclusions**: Given the present coverage in Mexico, it is necessary to optimize our resource allocation to improve the country's breast cancer prevention policy. (REV INVES CLIN. 2016;68:184-92)

Key words: Cost-effectiveness. Breast cancer. Mammography.

INTRODUCTION

Breast cancer (BrCa) is the most prevalent tumor among women worldwide, being the first cause of death from cancer in this population group[1]. Detection programs addressed at receiving medical attention in early stages are of the utmost importance to reduce the global burden of this disease. However, the benefits of mammography as a screening method in asymptomatic people have been controversial.

In Mexico, mammography coverage is below that recommended by the World Health Organization (WHO) for an effective screening program[2]. According to the 2011 National Health and Nutrition Survey (ENSANUT)[3], 10.9 and 18.0% of women 40-49 and 50-69 years old, respectively, reported to have had a mammographic screening[4]. Additionally, it is estimated that 2,699,752 (95% CI: 2,503,582-2,895,922) mammography screenings were performed in Mexico in 2011. Of these, 1,694,230 were conducted in women over the age of 50, i.e. 15.24% of women

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over 50 years old in Mexico reported having a mammography during 2011. According to the ENSANUT 2012, mammography screening in Mexico was used during 2011 mostly for prevention rather than for diagnostic purposes; of all women who self-reported having a mammography, 18% had had symptoms before their screening, while the rest (82%) were asymptomatic. It is also estimated that in 2011, 28,700 (1.3%) of 2,142,618 asymptomatic women who had a mammographic screening received a positive result.

Within this context of scarce coverage due to the lack of an organized screening program, in addition to poor access to adequate diagnosis and treatment, as previously described[5], it is necessary to identify the scenario in which the application of mammography in the Mexican population could be more effective. In this paper, we attempted to estimate the cost-effectiveness of different possible scenarios of BrCa screening using the methodology proposed by the WHO[6]. We present results from different scenarios, depending on the female population structure in Mexico, program periodicity schedule, reached coverage, and mammography sensitivity adjusted for age group.

METHODS

Study design

We performed a cost-effectiveness analysis in line with the WHO-CHOICE methodology[6]. The analysis consisted of a comparison of all plausible screening programs compared to a scenario in which there is no early detection program, defined as the null scenario. Different screening programs were simulated using a population model for a period of 10 years beginning in 2016. Each scenario accounts for a specific screening coverage for women of ages 25-75, divided in age groups of five-year class intervals. Additionally, three possible screening frequencies were taken into account: yearly, every two years, and every three years.

The population model shown in figure 1 simulates the epidemiology of BrCa in the country, considering transitions from a healthy state to a disease state, death, or survival. Three stages were considered for BrCa pooling all four known clinical stages (Fig. 1). Each stage will have an observed distribution depending on the screening program, e.g. increasing coverage will decrease stage III and increase stage I prevalence. Demographic data were obtained from the Mexican National Population Council (CONAPO, for its acronym in Spanish, Consejo Nacional de Población), which also takes into account births and background mortality[7]. The incidence of BrCa was simulated using age group-adjusted annual incidence rates based on regional estimates[1,8] (Table 1).

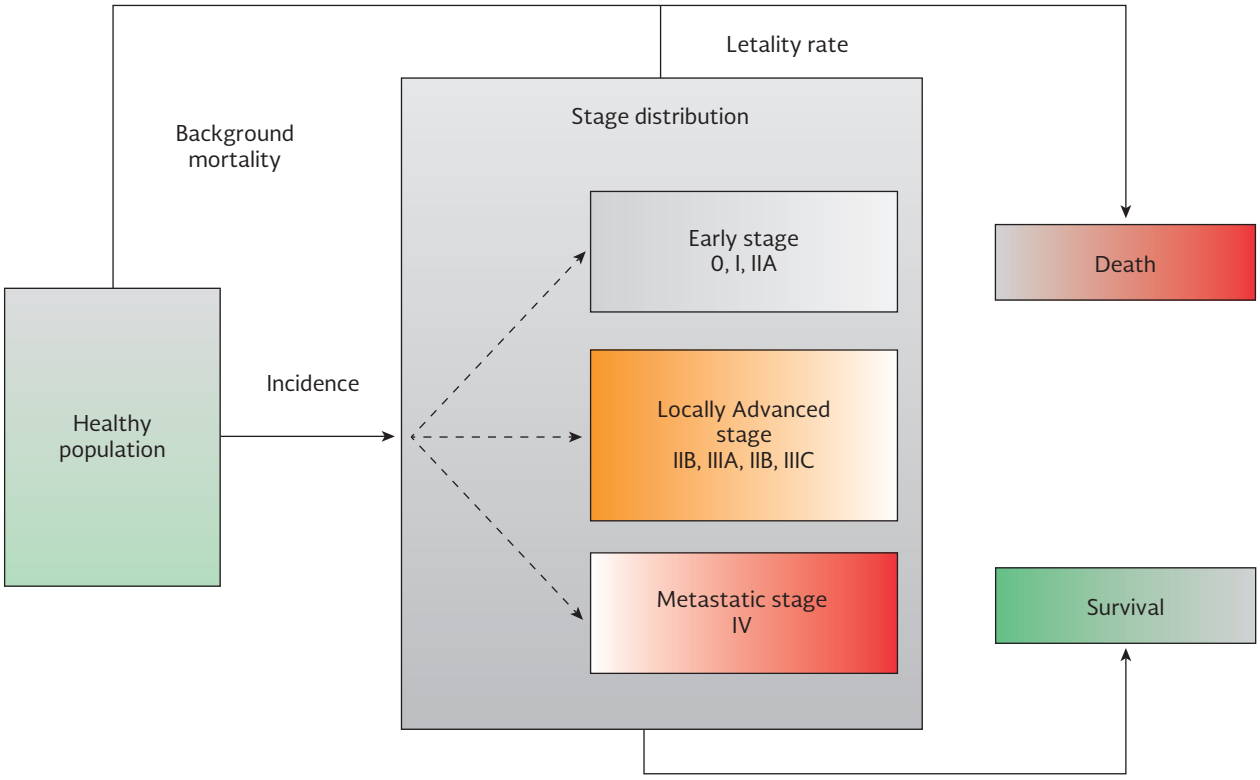
Transitions from BrCa to a death or survival state were simulated based on estimated BrCa stage-adjusted fatality rates derived from a patient cohort (n = 615) treated at the National Cancer Institute of Mexico (INCan, for its acronym in Spanish, Instituto Nacional de Cancerología), covered financially by the Catastrophic Expenditure Protection Fund (in Spanish, Fondo de Protección de Gastos Catastróficos, Seguro Popular), and followed up from 2007 to 2013[4]. The model assumes that a patient surviving more than five years will live to the age expectancy of 77.5 years, according to the Mexican National Institute of Statistics and Geography (INEGI, for its acronym in Spanish, Instituto Nacional de Estadística y Geografía)[9]. Additionally, women's age was estimated using the midpoint value of the five-year class interval (age) to which they belong.

Based on the described model, scenarios were simulated based on all possible combinations of coverage by age group and frequency shown in table 1. These scenarios were then compared to the null scenario to determine the most cost-efficient screening program.

Detection parameters

The mammography detection rate and proportion of screening-detected tumors were modeled following the method proposed by Duffy and Gabe[10]. According to Bray, et al.[8], these two variables depend on the mammogram's sensitivity and the BrCa latency period. The proportion of screen-detected tumors was estimated based on Tabar, et al.[11], who conducted a study of Swedish women between the ages of 40 and 74 (n = 133,000) with a follow-up period of 20 years. The mammogram's sensitivity was estimated based on Ohta, et al.[12], who carried out a detection program using mammography in Japanese women between 40-80 years old (n = 62,447). Finally, the latency

Figure 1. Population model used in the simulation. Arrows represent the transition from one state to another.



period of BrCa and the mammogram's sensitivity were linearly extrapolated for the 25-40 years age group[3]. Table 1 shows the latency period in years and the age group-adjusted mammogram's sensitivity.

Reproducibility

The analysis was performed using the R statistical software. Data analysis can be reproduced in its totality using the code, data sets, and markdown files[4,13].

Effectiveness

Following the WHO's methodology[6], the effectiveness of each detection scheme is measured in the number of disability-adjusted life years (DALY) averted in comparison to the null scenario. For each individual, a DALY is composed of years lost due to disability (YLD) and years of life lost (YLL) due to premature mortality[14]. The morbidity component (YLD) is computed as follows:

$$YLD = DW \times \int_{A}^{A+L} e^{-r(x-a)}\, dx$$

Where a is the age at which the disease was diagnosed (assigned); A and L are the age at onset and duration of the disease, respectively; r is the discount rate proposed by the WHO (6), and, finally, DW represents the disability weight which ranges between 0 and 1, where 0 represents a perfect health condition and 1 represents death. Disability weights corresponding to the three different cancer stages (Table 2) were obtained from the European Disability Weights Project[15]. Women who survived cancer were assigned a disability weight corresponding to mastectomy[16] until death. Each YLL is defined using the same equation setting DW = 1 and L accounts for the expected remaining years at the moment of death. The rest of the parameter definitions remain the same. The following equation was used for estimating DALY:

$$DALY = \tau\,(YLL) + (1-\tau)\,YLD,$$

where is the disease fatality rate.

Each DALY depends on the clinical stage of BrCa and the age of the individual. Table 2 shows the parameters used to estimate the effectiveness of each screening

Table 1. Input parameters for simulation

Age group	Incidence rate per 100,000 women[14]	BrCa latency period (in years)[9]	Mammogram's sensitivity[10]	Possible screening coverage
25-40	11.7	2.1	0.611	0, 1, 2%
40-45	58.7	2.4	0.698	0, 5, 10, 15%
45-50	84.3	2.4	0.698	0, 6, 12, 18%
50-55	106.5	3.7	0.667	0, 5, 10, 15, 20%
55-60	118.6	3.7	0.667	0, 5, 10, 15, 20, 25%
60-65	119.4	4.2	0.773	0, 5, 10, 15, 20%
65-70	116.6	4.2	0.773	0, 6, 12, 18%
70-75	108.8	4.0	0.838	0, 2%
Periodicity	–	–	–	Every 1, 2 or 3 years

For each age group stratified by groups of five years, columns 2 to 4 detail the population parameters used to estimate the detection rates from the mammography. Column 5 lists the possible coverage values assessed in the simulations.
BrCa: breast cancer.

Table 2. Estimated survival probabilities and disability weights

Estimated survival probabilities[3]	Early stage	Locally advanced	Metastatic
First year	0.99	0.97	0.69
Second year	0.97	0.88	0.41
Third year	0.93	0.74	0.20
Fourth year	0.88	0.58	0.08
Fifth year	0.82	0.43	0.02
Disability weights[13]	–	–	–
First year of disease	0.27	0.37	0.61
Second to fifth year	0.18	0.30	0.61
Death	1.0	1.0	1.0
Survival	0.05	0.05	0.05

Estimated survival probabilities and disability weights for each breast cancer clinical stage. These parameters were used to quantify the burden of disease for each breast cancer status.

scheme. Each program will have an amount of DALYs associated to it. According to the WHO method, the effectiveness of each screening program is defined as the difference of DALYs in comparison to the null scenario. That is, the number of DALYs averted is estimated as:

$$DALYS\ AVERTED_{Program\ j} = DALYS_{Null\ Scenario} - DALYS_{Program\ j}$$

Costs

In line with the WHO-CHOICE approach[4], patient and program treatment costs were identified. Stage-adjusted cancer treatment costs were obtained from the Reimbursement Tabulator of the INCan's Catastrophic Expenditures Protection Fund[17]. Mammography costs include a depreciation of the mammogram, use of electricity, use of building space, and radiologist wages according to the Costs Tabulator from the Office of Diagnostic and Treatment Ancillary Services of Mexico's National Cancer Institute. Transportation and opportunity costs were not taken into account. An inflation rate of 3% was assumed. Table 3 details the costs used in the model. The cost of a screening program is compared to the cost in the null scenario:

$$ADDITIONAL\ COST_{Program\ j} = TOTAL\ COST_{Program\ j} - TOTAL\ COST_{Null\ Scenario}$$

Cost-effectiveness analysis

Averages of the total costs and DALYs averted for the 10-year simulation period were calculated for every

Table 3. Costs associated with breast cancer screening in Mexican Pesos 2015

	Asymptomatic women	Early stage	Locally advanced stage	Metastatic stage
Treatment cost[15]	–	$176,733.30	$245,933.50	$264,355.80
Mammography cost[15]	$1,186.00	–	–	–

Costs of mammography and treatment used to estimate the costs of each screening program.

screening program to obtain the following average cost-effectiveness ratio (ACER):

$$ACER_{Program\ j} = \frac{AVERAGE\ OF\ ADDITIONAL\ COSTS_{Program\ j}}{AVERAGE\ OF\ DALYS\ AVERTED_{Program\ j}}$$

Having estimated the ACER for all possible interventions with respect to the null scenario, we defined the expansion route as a series of programs that could be potentially implemented by increasing the available budget. This expansion path is obtained calculating the ACER for all programs in comparison with the current intervention, and choosing the one with the lowest ratio. Starting from the null scenario on, this procedure results in the corresponding expansion path shown in figure 2[4].

Finally, in line with the WHO-CHOICE methodology[6], scenarios in which each DALY averted is strictly less than three-times the GDP per capita are defined as cost-effective, and those whose cost per DALY is strictly less than the GDP per capita as highly cost-effective. In the case of Mexico, these limits are $10,307 and $30,921 per DALY averted[18].

RESULTS

Estimation of DALYS averted by cancer stage and age group at an individual level is shown in table 4. Results of the analysis show that the current scenario is highly cost-effective, with an average of 10,741 DALYs averted per year. As shown in figure 2, the expansion path suggests implementing a feasible program with an ACER lower than that of the current program. As the best option, this screening program implies a frequency of once every three years with the coverage described in table 4; it increases the coverage in age groups between 40-70 years, specifically in the five-year class interval age group of 55-60 years, and would, additionally, result in average savings of 31 million dollars per year leading to 448 DALYs averted. Finally, if the annual budget were to increase 9 million dollars per year compared to the current intervention, the objective program shown in figure 2 would be feasible. Thus, the objective intervention consists of a periodic program schedule every two years with the coverage shown in table 4, which would result in 12,696 DALYs averted, representing an increase of 1,995 compared to the current program.

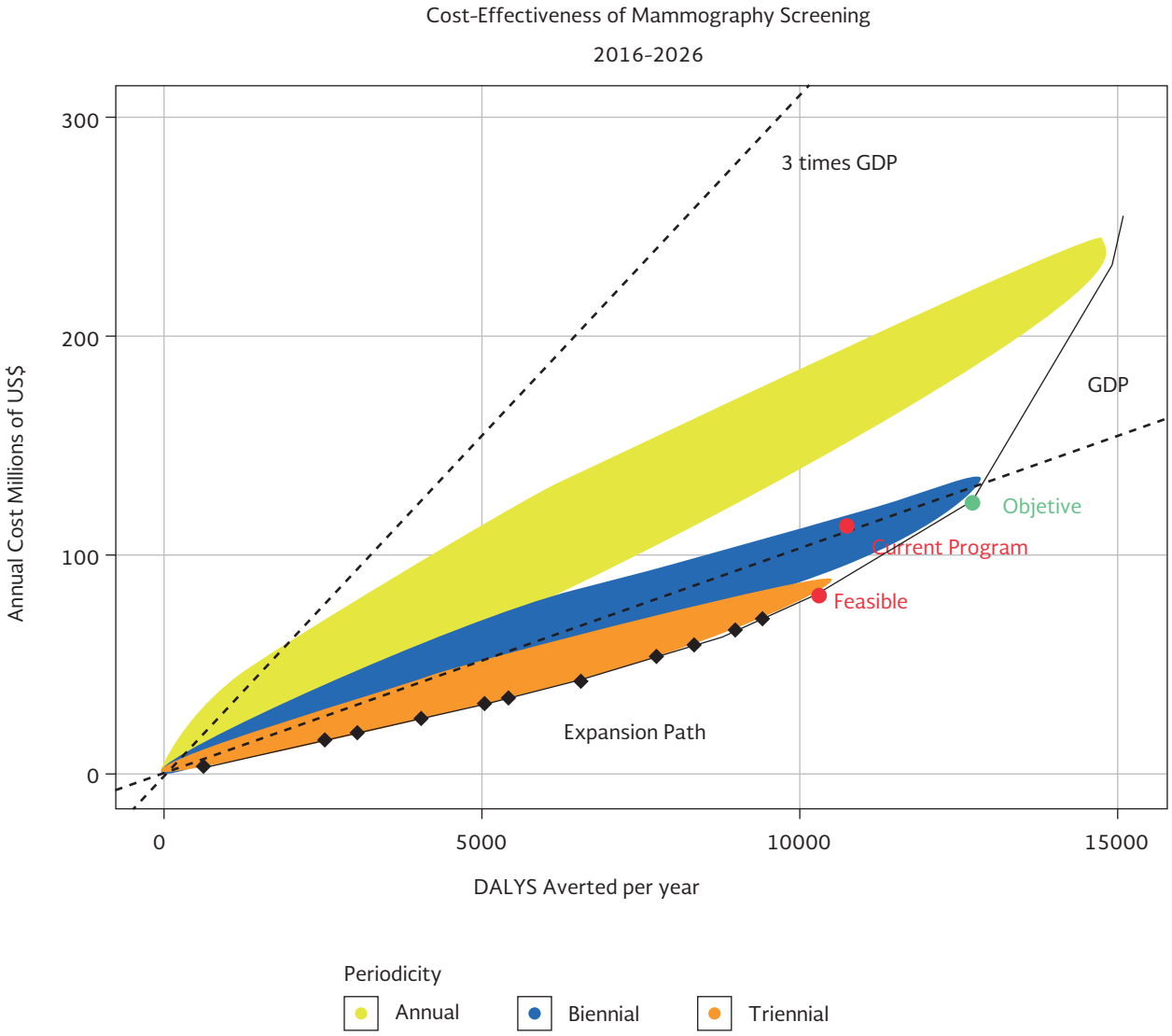
Sensitivity analysis

Following the WHO-CHOICE methodology, the discount rate was removed () for the estimation of DALYs averted per year. The feasible and objective programs were kept with the same coverage, but their frequency was changed to every two years and every year, respectively[4]. In a separate analysis, the latency period of BrCa and the mammography sensitivity were adjusted according to Taghipour, et al.[19], resulting in the same feasible and objective scenarios shown in figure 2, although the DALYs averted decreased considerably to 9,818 and 12,204, respectively[4]. In addition, the current program shifted from the region of highly cost-effective to cost-effective programs.

DISCUSSION

The WHO resolution on Cancer Prevention and Control (WHA58.22) recommends low- and middle-income countries to identify evidence-based, sustainable actions to improve cancer care and to make the best use of their resources to benefit the cancer-afflicted population[20]. Given Mexico's current resources, it is necessary to identify the best practices in prevention, early detection, and treatment for BrCa. According to Anderson, et al.[19], early detection efforts in low- and middle-income countries can be segmented according to the level of available resources. Mexico's current goal should be to reduce the proportion of the population with symptomatic disease through the use of

Figure 2. Results from the simulation; the x-axis shows the total disability-adjusted life years averted per year for each simulated program and the y-axis shows its approximate cost. Any program between the 3 x GDP and GDP threshold is considered to be cost-effective. The highly cost-effectiveness region is under the GDP dotted-line threshold. The expansion path is shown in grey and includes the most highly cost-effective feasible screening program in orange and the optimal program in green. The current screening program is shown in red.



mammography as an early screening method in target groups, along with an improvement in the quality of the imaging techniques and interpretation, appropriate monitoring of the population to identify the current incidence of interval breast cancers, and, of course, ensuring access to timely and appropriate treatment.

Nevertheless, the Mexican Official Standard[21] for breast cancer prevention, diagnosis, treatment, control, and epidemiological surveillance states that all women over the age of 50 should have a mammography once a year, and that women between 40-49 years old with two or more risk factors should have a mammography every two years, corresponding to an enhanced level of resources according to the guideline for breast healthcare in low- and middle-income countries[20]. This suggests that Mexico should adjust its current Official Standard to more realistic goals.

Table 4. Results from simulation

Age Group	DALYs adjusted for BrCa stage and age group			Screening programs		
	DALYs Early	DALYs Locally advanced	DALYs Metastatic	Current program*	Feasible program	Objective program
25-40	5.52	13.84	23.42	1.9%	0%	0%
40-45	4.86	12.05	20.46	9.6%	15%	15%
45-50	4.44	10.93	18.61	14.5%	18%	18%
50-55	3.95	9.64	16.45	19.6%	20%	20%
55-60	3.39	8.13	13.95	18.9%	25%	25%
60-65	2.74	6.38	11.05	17.9%	20%	20%
65-70	1.98	4.34	7.68	14.5%	18%	18%
70-75	1.09	1.98	3.76	7.3%	0%	0%
Frequency	–	–	–	Every two years	Every three years	Every two years
DALYs averted per year	–	–	–	10,741	10,293	12,696

Results obtained from the simulations. For each age group stratified by groups of five years, columns 2 to 4 show the estimated DALYs for each breast cancer clinical stage. Column 5 provides an estimate of the DALYs averted by the current screening program in Mexico based on the National Health and Nutrition Survey2. Column 6 details the optimal economically feasible screening coverage and the total of DALYs averted. Column 7 displays the optimal screening program in the highly cost effective region.
*Estimated based on the National Health and Nutrition Survey 2012 (Instituto Nacional de Salud Pública)[2]
DALY: disability-adjusted life year.

Our findings suggest that in Mexico, the use of mammography as a screening method for women is highly cost-effective only when the periodicity program schedule is every three or every two years for particular programs, and when coverage includes only women from the age group of 40-70 years, resulting in fewer unnecessary biopsies and a decrease in over-diagnosis and false positives (mainly in women under the age of 50 for whom the test is less sensitive and reliable). A frequency of every three years has also been defined as cost-effective in studies from Australia and New Zealand in women aged between 50-70 years[22], and countries with similar conditions to those in Mexico, such as Peru[23]. According to the International Agency for Research on Cancer[24], there is sufficient evidence that mammography can be cost-effective for women aged 50-75 in countries with high incidence rates, yet there is limited evidence to demonstrate that mammography is cost-effective in low- and middle-income countries. Notwithstanding, studies from Valencia-Mendoza, et al.[25] and Niëns, et al.[26] support the idea that screening interventions in Mexico using mammography are cost-effective according to the WHO-CHOICE criteria. The expansion path in figure 2 suggests that as the budget increases, priority should be given to the age group of 60-70 years. Clinical breast examination was not taken into consideration, but is known to shift the stage distribution to a lower stage and could be less expensive[24]. The probably underestimated prices of mammography and treatment, and the assumptions that the detection parameters are valid in Mexican women even though the studies were conducted abroad, may be additional study limitations. However, these variables were applied equally to all simulated scenarios. A lack of literature regarding the mammogram's sensitivity and the estimation of the latency period of BrCa in Mexican women suggests the need for further studies in this area. Since the model is population-based, it does not take into account additional risk factors such as physical activity, weight control, and hormone therapy. Furthermore, the population model does not account for over-diagnosis or false positives that are known to lead to psychological consequences[25]. One of the strengths of the simulation is its relatively low population coverage levels, which are close to the percentages reported for the current screening[3]. If they were to be implemented, this restriction allows a relative feasibility of the programs.

In conclusion, from a health policy perspective, it is necessary to optimize the scarce resources available for prevention, implementing an organized prevention program targeting a specific population age group, preferably women between 40-70 years of age, with regular monitoring every three years. However, this intervention would only be truly useful if diagnostic, referral, treatment, and basic palliative services were simultaneously improved, and access to such services was improved by reducing existing barriers.

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PERMANYER

Rev Inves Clin. 2016;68:193-202 ORIGINAL ARTICLE

Clinical, Dialytic, and Laboratory Factors Associated With Poor Health-Related Quality of Life in Mexican Patients on Hemodialysis

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ABSTRACT

Background: End-stage renal disease and its treatment have a negative impact on the quality of life of patients. **Objective:** To determine the clinical, dialytic, and laboratory factors associated with poor health-related quality of life in Mexican patients on hemodialysis. **Methods:** A multicenter, cross-sectional study. The KDQOL-SF36 v1.3 questionnaire was applied to patients with end-stage renal disease on hemodialysis in different regions of Mexico. Patients were classified according to their overall score on the questionnaire: poor health-related quality of life (overall score below the median) or good health-related quality of life (overall score above the median). Clinical, dialytic, and laboratory variables associated with poor health-related quality of life were analyzed using linear correlation and multivariate logistic regression. **Results:** We included 194 adult patients with a median age of 55 (45-64) years. The diagnosis of poor health-related quality of life was present in 47.4% of patients. A poor correlation was found between the clinical, dialytic, and biochemical parameters and the health-related quality of life score (range of correlations r = –0.4 to 0.2). Serum albumin level showed the highest number of weak, statistically significant correlations. Factors associated with poor health-related quality of life in the multivariate analysis were: time spent on hemodialysis (OR = 1.02; 95% CI; 1.00-1.04; p = 0.02), use of a venous catheter (OR = 3.2; 95% CI: 1.36-7.75; p = 0.01), and serum albumin < 4 g/dl (OR = 3.55; 95% CI: 1.44-8.74; p < 0.01). **Conclusions:** Poor health-related quality of life was common in Mexican patients undergoing hemodialysis. No strong correlation was found between the clinical, dialytic, or laboratory factors with health-related quality of life. Factors associated with poor health-related quality of life were: time on hemodialysis, use of a venous catheter, and serum albumin level < 4 g/dl. (REV INVES CLIN. 2016;68:193-202)

Key words: HRQoL. Quality of life. KDQOL-SF36. Hemodialysis.

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INTRODUCTION

In Mexico, similar to the rest of the world, end-stage renal disease (ESRD) is a public health problem due to its high prevalence, morbidity, mortality, and economic costs arising from medical care[1-9]. Additionally, it has been consistently demonstrated that ESRD and its treatment produces a negative impact on the quality of life of patients with this disease[10,11]. Moreover, the evaluation of the health-related quality of life (HRQoL) is a relatively new concept in the field of nephrology, but it is becoming increasingly important due to its role as an independent predictor of clinical outcomes[12] and as a key indicator in the evaluation of the quality of health care[13]. However, despite the current trend of including the evaluation of HRQoL as an important measure of medical care, studies evaluating the HRQoL of patients with ESRD undergoing hemodialysis are scarce. The aim of our study was to evaluate the HRQoL of patients and determine the clinical, dialytic, and laboratory factors associated with poor HRQoL (P-HRQoL) in Mexican patients with ESRD who are undergoing hemodialysis.

MATERIALS AND METHODS

We performed a cross-sectional study. The Institutional Research and Ethics Committee reviewed and approved the protocol. A version of the Kidney Disease Quality of Life Short Form (KDQOL-SF36 v1.3) questionnaire was administered by an interviewer to 194 adult patients with ESRD who were receiving chronic hemodialysis in different regions of Mexico. We included clinically stable patients with more than one month of dialysis treatment. We excluded patients with any physical disability. Patients were grouped according to their overall score as patients with a P-HRQoL (overall score of the questionnaire below the median score of the general group) and patients with a good HRQoL (G-HRQoL, overall score above the median score of the general group). Clinical (age, sex, comorbidities, and education), dialytic (type of vascular access, time on hemodialysis, and Kt/V), and laboratory (hemoglobin, serum calcium, serum phosphorus, and serum albumin levels) variables were collected and compared between groups. Descriptive statistics with means/standard deviations and medians/25-75th percentiles were used to describe continuous variables according to distribution data; frequencies and proportions were used to describe categorical variables. Comparisons between the two groups were performed using Student's *t* test or Mann-Whitney *U* test according to distributions of data in the case of continuous variables and by a X^2 test in the case of categorical variables. We used one-factor ANOVA for comparisons between more than two groups. Correlations between dialytic, laboratory variables and the HRQoL scores were done using the Spearman correlation coefficient. Risk factors associated with HRQoL scores were analyzed by multivariate logistic regression. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 194 adult patients with ESRD who were undergoing chronic hemodialysis were included, of whom 37.6% (n = 73) lived in the northern region, 28.9% (n = 56) lived in the southern region, and 33.5% (n = 65) lived in the central region of Mexico. Median age was 55 (45-64) years, and 54.6% (n = 106) of the patients were male. The most frequently observed comorbidities included hypertension in 86.6% (n = 168), diabetes mellitus type 2 in 57.2% (n = 111), and dyslipidemia in 7.2% (n = 14) of patients. Regarding the educational level of our population, 12.4% (n = 24) were illiterate, 41.8% (n = 81) had a complete primary education, and 16.5% (n = 32) had a professional education. The main causes of ESRD were type 2 diabetes mellitus in 48.5% (n = 94) of patients and hypertension in 15.5% (n = 30); in 14.9% (n = 29), the cause was unknown. In addition, 75.3% (n = 146) of patients did not perform any type of paid work. In 55.2% (n = 107) of patients, vascular access was achieved with a catheter, and in 44.8% (n = 87) an arteriovenous fistula was used. The median time on hemodialysis was 19 (8-38) months. The medians (25-75 percentiles) of factors studied were: hemoglobin 10.5 (9.1-11.7) g/dl, calcium 8.7 (8.0-9.2) mg/dl, phosphorus 5.8 (4.8-7.3) mg/dl, serum albumin 4.0 (3.7-4.3) g/dl, Kt/V 1.2 (1.0-1.4), and 250 (20-600) ml/day for residual urine volume.

Comparison of clinical, dialytic, and laboratory characteristics between patients with good and poor health-related quality of life

The median overall score of HRQoL of our population was 55.6 points. A total of 47.4% (n = 92) of patients had a diagnosis of P-HRQoL according to the criterion used (the median score). When comparing general characteristics of patients with P-HRQoL and G-HRQoL, we observed that age was lower in patients with G-HRQoL (53 vs. 59 years; p = 0.03), the mean of time on hemodialysis was higher in patients with G-HRQoL, and the proportion of patients with type 2 diabetes mellitus was higher (65.2 vs. 50.0%; p = 0.03) in the group with P-HRQoL. In addition, the proportion of patients with an arteriovenous fistula was higher for patients in the G-HRQoL group (52.9 vs. 35.9%; p = 0.01). The proportion of patients with serum phosphorus levels greater than 5.5 mg/dl (45.6 vs. 66.3%; p = 0.01) was lower in patients with P-HRQoL. The proportion of patients with normal serum phosphorus levels was higher (50.6 vs. 28.3%; p = 0.01) in patients with P-HRQoL vs. G-HRQoL. Moreover, serum albumin levels (3.9 vs. 4.1 g/dl; p = 0.02) and the proportion of patients with serum albumin levels greater than 4.0 g/dl (40.5 vs. 64.3%; p = 0.001) were lower in patients with P-HRQoL compared with G-HRQoL. For the remaining clinical, dialytic, and laboratory characteristics shown in table 1, no statistically significant differences were found between groups.

Comparison of health-related quality of life between patients with end-stage renal disease undergoing hemodialysis and healthy patients

The mean overall score of the KDQOL-SF36 v1.3 questionnaire was 56.5 ± 11.0 points, with a minimum score of 25.6 and a maximum of 84.4 points. The most affected dimensions of the specific disease component (KDQOL component) of the questionnaire were the quality of social interaction (21.0 ± 20.9 points), cognitive dimension (21.8 ± 21.7 points), and work (33.7 ± 37.1 points). In the generic component (SF36 component) of the questionnaire, the most affected dimensions were physical role (25.9 ± 37.7), emotional role (37.8 ± 38.2), and general health perception (48.5 ± 23.0). We compared scores of the SF36 generic component of the KDQOL-SF36 with the scores of the QOL SF36 questionnaire obtained from healthy Mexican adults in a nationally representative sample reported by Duran, et al., which included 5,961 Mexican healthy individuals over 25 years old selected through multistage sampling covering rural and urban areas of Mexico[14]. We observed that Mexican patients with ESRD on hemodialysis had a lower score in all evaluated dimensions of quality of life, except for the dimension of emotional well being, in which the scores were similar (Table 2). On the other hand, patients with P-HRQoL had lower scores in all dimensions including the physical and mental component of QOL SF36 compared to patients with G-HRQoL and the healthy population. Finally, patients with G-HRQoL had lower scores on the physical and mental component of QOL SF-36 compared to healthy patients. However, these low scores were mainly attributed to physical functioning, role emotional, and role physical dimensions. In other dimensions of the SF36 component, the scores of G-HRQoL were very similar to the scores observed in the healthy population reported by Duran, et al. (Table 2).

Comparison of dimensions of health-related quality of life between patients with poor and good health-related quality of life

We compared the dimensions of HRQoL between patients with P-HRQoL and G-HRQoL in our population. We observed that in the specific disease component of the questionnaire (KDQOL component), patients with P-HRQoL had a lower score in most dimensions, particularly in the dimensions of burden of chronic kidney disease (CKD) (26.1 vs. 54.3; p < 0.01), work (22.8 vs. 43.6; p < 0.01), and the effect of CKD (53.2 vs. 71.6; p < 0.01). In contrast, patients with P-HRQoL had a higher score in the cognitive (28.2 vs. 16.1; p < 0.01) and quality of social interaction (25.7 vs. 16.7; p < 0.01) dimensions. No statistically significant differences were observed in the dimensions of support from the dialysis team (92.2 vs. 89.8; p = 0.34) and satisfaction with dialysis care (78.6 vs. 80.7; p = 0.49) among patients with G-HRQoL and P- HRQoL (Table 2).

In the generic component of the questionnaire (SF-36 component), patients with P-HRQoL had a lower score on most dimensions. This was especially seen in the physical role (4.0 vs. 45.8; p < 0.01), emotional role (18.1 vs. 55.5; p < 0.01), and pain (52.7 vs. 85.3;

Table 1. Comparison of clinical, dialytic, and laboratory characteristics between patients with poor and good health-related quality of life

Variables	P-HRQoL		G-HRQoL		p
	n = 92	%	n = 102	%	
Age (Md; 25-75p)		59 (48-68)		53 (43-60)	0.03
Male/female		52.2/47.8%		56.9/43.1%	0.51
Diabetes mellitus	60	65.2%	51	50%	0.03
Vascular access:					
Catheter	59	64.1%	48	47.1%	0.01
Arteriovenous fistula	33	35.9%	54	52.9%	
Time on hemodialysis (Md)		14 (5-34)		24 (12-36)	0.02
Kt/V (median)		1.2 (0.9-1.4)		1.2 (1.0-1.3)	0.94
Kt/V < 1.4	61	75.3%	74	79.6%	0.5
Kt/V > 1.4	20	24.7%	19	20.4%	
Hemoglobin (Md; 25-75p)		10.4 (8.9-11.6)		10.6 (9.3-11.9)	0.61
Hb < 9 g/dl	26	28.5%	18	17.6%	0.19
Hb 9-11 g/dl	33	36.3%	43	42.2%	
Hb >11 g/dl	32	35.2%	41	40.2%	
Serum calcium (Md; 25-75p)		8.8 (8.1-9.2)		8.6 (8.0-9.4)	0.58
Ca < 8.5 mg/dl	33	41.2%	38	40.8%	0.15
Ca 8.5-10 mg/dl	38	47.5%	33	35.5%	
Ca > 10 mg/dl	9	11.3%	22	23.7%	
Serum phosphorus (Md; 25-75p)		5.4 (4.5-6.6)		6.2 (5.3-7.9)	0.13
P < 3.5 mg/dl	3	3.8%	5	5.4%	0.01
P 3.5-5.5 mg/dl	40	50.6%	26	28.3%	
P > 5.5 mg/dl	36	45.6%	61	66.3%	
Serum albumin (Md; 25-75p)		3.9 (3.5-4.2)		4.1 (3.8-4.3)	0.02
Albumin < 4 g/dl	50	59.5%	35	35.7%	0.001
Albumin > 4 g/dl	34	40.5%	63	64.3%	

Md: median; 25-75p: 25-75th percentile; HRQoL: health-related quality of life; P: poor; G: Good.

p < 0.03) dimensions, as well as the physical (32.2 vs. 43.5; p < 0.01) and mental components (41.3 vs. 51.7; p < 0.01) (Table 2).

Correlation between clinical, dialytic, and laboratory parameters and health-related quality of life in patients with end-stage renal disease undergoing hemodialysis

A poor correlation was observed between most clinical and biochemical parameters and the dimensional scores and overall score of HRQoL. Serum albumin level was the parameter with the highest number of statistically significant correlations. However, it showed a weak positive correlation with physical function (r = 0.2; p = 0.01), energy/fatigue (r = 0.3; p = 0.01), and the overall score of HRQoL (r = 0.2; p = 0.01). It also exhibited a weak negative correlation with cognitive function (r = –0.2; p = 0.01). Age showed a negative correlation with the physical dimensions (physical function: r = –0.4, p = 0.01; physical role: r = –0.2, p = 0.01) and the overall score of HRQoL (r = –0.2; p = 0.01). The Kt/V only exhibited a weak negative correlation with the sleep dimension (r = –0.2; p = 0.01) of the HRQoL, and time on hemodialysis showed a weak negative correlation with general health perception (r = –0.1; p = 0.01) and positive correlation with social function (r = 0.2; p < 0.01). The remaining correlations are shown in table 3.

Clinical, dialytic, and laboratory factors associated with poor health-related quality of life in patients with end-stage renal disease undergoing hemodialysis

In the multivariate logistic regression, the independent risk factors associated with P-HRQoL in Mexican

Table 2. Comparisons of health-related quality of life between healthy Mexican subjects and poor and good health-related quality of life patients with end-stage renal disease on hemodialysis

	Healthy*	General	P-HRQoL	G-HRQoL	p
KDQOL component					
Symptom/problem list	–	78.9	72.4	84.8	< 0.01
Effects of kidney disease	–	62.9	53.2	71.6	< 0.01
Burden of kidney disease	–	40.9	26.1	54.3	< 0.01
Work status	–	33.7	22.8	43.6	< 0.01
Cognitive function	–	21.8	28.2	16.1	< 0.01
Quality of social interaction	–	21.0	25.7	16.7	< 0.01
Sexual function	–	79.7	70.3	87.1	< 0.01
Sleep	–	62.3	58.1	66.1	< 0.01
Social support	–	69.0	64.3	74.0	0.03
Dialysis staff encouragement	–	90.9	92.2	89.8	0.34
Patient satisfaction	–	79.7	78.6	80.7	0.49
SF-36 Component					
Physical functioning	89.6	53.1	36.9	67.7	< 0.01†,‡,#
Role physical	88.7	25.9	4.0	45.8	< 0.01†,‡,#
Pain	85.5	69.8	52.7	85.3	< 0.01†,‡
General health	52.2	48.5	36.8	59.0	< 0.01†,‡,#
Emotional well-being	72.1	72.8	60.4	84.0	< 0.01†,‡,#
Role emotional	88.9	37.8	18.1	55.5	< 0.01†,‡,#
Social function	75.1	69.7	54.7	83.2	< 0.01†,‡,#
Energy/fatigue	70.7	61.9	48.4	74.0	< 0.01†,‡,#
Overall score	–	56.57	47.1	65.0	< 0.01
SF-12 physical	79.0	38.2	32.2	43.5	< 0.01†,‡,#
SF-12 mental	76.7	46.8	41.3	51.7	< 0.01†,‡,#

T-Student test between P-HRQoL vs G-HRQoL was used in the KDQOL component and overall score of KDQOL SF36.
ANOVA test between P-HRQoL, G-HRQoL and Healthy was used in the SF36 component.
*Score obtained from healthy Mexican patients in a nationally representative sample[14]; †P-HRQoL vs. G-HRQoL; ‡P-HRQoL vs. healthy; #G-HRQoL vs. healthy.
KDQOL: Kidney Disease Quality of Life; SF: short form; P-HRQoL: poor health-related quality of life; G-HRQoL: good health-related quality of life.

patients on hemodialysis were time spent on hemodialysis (OR = 1.02; 95% CI: 1.00-1.04; p = 0.02), the use of a venous catheter vs. arteriovenous fistula (OR = 3.2; 95% CI: 1.36-7.75; p = 0.01), and serum levels of albumin below 4 g/dl (OR = 3.55; 95% CI: 1.44-8.74; p < 0.01). The remaining clinical, dialytic, and laboratory factors included in the multivariate analysis shown in table 4 were not associated with P-HRQoL in our population.

DISCUSSION

Based on the results of our study, we can confirm that Mexican patients on hemodialysis have a marked decrease in their quality of life. When we compared scores of the SF36 generic component of the KDQOL-SF36 with the scores of the QOL SF36 questionnaire obtained from healthy Mexican adults in a nationally representative sample[14], hemodialysis patients showed a marked decrease in the scores of physical (38.1 ± 10.0 vs. 79.0 ± 0.2; p < 0.01) and mental (51.7 ± 7.8 vs. 76.7 ± 0.2; p < 0.01) components of QOL SF36. This decrease was more pronounced in the physical role (25.9 vs. 88.7; delta = −62.8 points), emotional role (37.8 vs. 88.9; delta = −51.1 points), and physical function (53.1 vs. 89.6; delta = −36.5 points) dimensions. In the medical literature, it has been consistently documented that ESRD and its treatment with hemodialysis or peritoneal dialysis produces a negative effect on the quality of life of these patients. Pagels, et al. conducted a study to evaluate the quality of life of patients with CKD in different stages and at the start of dialytic treatment. They included 535 patients with CKD stages 2-5 of the Kidney Disease Outcomes Quality Initiative (KDOQI) classification and

Table 3. Correlations between clinical, dialytic and laboratory factors with health-related quality of life

	Age	TH	Hb	Ca	P	Alb	Kt/V
KDQOL component							
Symptom/problem list	–0.099	0.119	0.059	–0.008	0.101	0.296*	–0.127
Effects of kidney disease	–0.136	0.036	0.160*	–0.005	0.167*	0.197*	0.041
Burden of kidney disease	–0.082	0.140	0.086	0.014	0.098	0.239*	–0.031
Work status	–0.114	0.140	–0.010	0.125	0.081	0.173*	–0.109
Cognitive function	0.064	–0.082	–0.071	–0.105	–0.152*	–0.284*	0.137
Quality of social interaction	–0.050	–0.071	–0.027	–0.098	–0.132	–0.218*	–0.047
Sexual function	–0.083	0.026	0.005	0.101	–0.076	0.032	0.034
Sleep	–0.198*	0.202*	0.110	0.024	0.072	0.278*	–0.208*
Social support	0.012	–0.101	0.101	–0.107	0.021	–0.040	0.055
Dialysis staff encouragement	0.045	–0.018	–0.116	0.078	–0.066	–0.095	0.092
Patient satisfaction	–0.071	–0.085	–0.005	–0.204*	0.006	–0.035	0.048
SF-36 component							
Physical functioning	–0.410*	0.088	0.217*	–0.015	0.196*	0.229*	0.106
Role physical	–0.236*	0.091	0.045	–0.005	0.174*	0.103	0.179*
Pain	–0.079	0.053	–0.023	0.012	0.147	0.234*	0.017
General health	0.045	–0.155*	0.168*	–0.002	0.070	0.024	0.070
Emotional well being	–0.122	0.155*	0.002	–0.007	0.184*	0.268*	–0.045
Role emotional	–0.096	0.079	0.115	–0.048	0.126	0.083	0.010
Social function	–0.097	0.217*	0.033	0.075	0.190*	0.221*	0.166*
Energy/fatigue	–0.134	0.198*	0.022	0.023	0.188*	0.310*	–0.024
Overall score	–0.263*	0.171*	0.131	0.017	0.190*	0.271*	0.021

KDQOL: Kidney Disease Quality of Life; SF: short form; P-HRQoL: poor health-related quality of life; G-HRQoL: good health-related quality of life; TH: time on hemodialysis (months); Hb: hemoglobin; Ca: serum calcium; P: serum phosphorus; Alb: serum albumin.
*$p < 0.05$ for Spearman correlation coefficient.

55 healthy control patients. Compared to the controls, a significant decline was observed in all dimensions of quality of life evaluated in patients with CKD, especially in the physical and general health dimensions, which were more pronounced in patients with more advanced stages of CKD (Stage KDOQI-5)[11]. These findings show that quality of life is affected even in patients with early stages of CKD, and is substantially impaired in patients with ESRD at the start of dialytic treatment. Furthermore, Brennan, et al. conducted a systematic review, including 47 studies, that evaluated the quality of life of patients with ESRD and compared the results to the quality of life of healthy control subjects. Patients with ESRD who received hemodialysis and peritoneal dialysis showed a significant decline in their quality of life compared to healthy subjects, especially in the physical, vitality, and, to a lesser degree, mental status dimensions, which demonstrates the negative effect of CKD and its treatment on the quality of life of these patients[10].

We performed a comparison of HRQoL scores between the different hemodialysis centers of our study. No statistically significant differences were found in the overall scores between hemodialysis patients of different regions of Mexico. However, in specific dimensions of KDQOL SF36 we observed differences between hemodialysis patients of different regions of our country (Table 5). Furthermore, when comparing the overall HRQoL score of our population (56.5) with that of patients with ESRD receiving hemodialysis reported in other countries, we observed that the score in Mexican patients was lower than that of patients in the USA (63.7), Europe (62.7), Japan (63.3), and Brazil (62.3) (Table 5)[15,16]. Similar to the results observed in other countries, the dimensions work and physical role in the quality of life component were the most affected in Mexican patients. However, the dimensions with lower scores in our population included quality of social interaction and cognition, which showed much lower scores than those observed for these dimensions in other countries. Such low scores observed in our population could be due in part to comprehension problems regarding the questions that evaluate these dimensions in the questionnaire. In contrast, the dimension of HRQoL with the highest score in our population

Table 4. Multivariate logistic regression analysis of clinical, dialytic and laboratory factors associated with poor health-related quality of life

Variables	OR	95% CI		p
		Lower	Upper	
Age (years)	1.02	0.99	1.05	0.18
Gender (male vs. female)	0.85	0.39	1.85	0.68
Diabetes mellitus (yes/no)	1.39	0.57	3.37	0.46
Vascular access (catheter vs. fistula)	3.25	1.36	7.75	0.01
Hemoglobin (9-11 g/dl reference)	1.00	-	-	-
Hemoglobin (< 9 g/dl)	1.62	0.55	4.73	0.37
Hemoglobin (> 11 g/dl)	1.79	0.72	4.40	0.20
Serum calcium (8.5-10.0 mg/dl reference)	1.00	-	-	-
Serum calcium (< 8.5 mg/dl)	0.61	0.25	1.50	0.28
Serum calcium (> 10 mg/dl)	0.32	0.10	1.03	0.06
Serum phosphorus (3.5-5.5 mg/dl reference)	1.00	-	-	-
Serum phosphorus (< 3.5 mg/dl)	0.48	0.06	3.83	0.49
Serum phosphorus (> 5.5 mg/dl)	0.49	0.22	1.08	0.07
Serum albumin (< 4 vs. > 4 g/dl)	3.55	1.44	8.74	< 0.01
Kt/V (< 1.4 vs. > 1.4)	0.99	0.38	2.55	0.98
Time on hemodialysis (months)	1.02	1.00	1.04	0.02

OR: odds ratio.

Table 5. National (between hemodialysis centers in our study) and international comparison of health-related quality of life of Mexican patients on hemodialysis

	National comparison					International comparison				
	Sinaloa	Veracruz	Puebla	SLP	p	Mexico	Europe	Japan	USA	Brazil
KDQOL component										
Symptom/problem list	73.0*	80.0*	80.9	87.1†	< 0.01	78.9	70.4	73.8	72.2	81.2
Effects of kidney disease	62.5	64.0	64.5	61.5	0.9	62.9	57.9	66.7	63.3	73.3
Burden of kidney disease	33.8*	49.3*	38.0	43.9	0.01	40.9	36.8	27.6	42.4	46.8
Work status	22.6†	38.4	37.5	45.1†	< 0.01	33.7	28.5	33.0	27.0	22.3
Cognitive function	22.1	21.3‡	35.0‡,#	14.5#	< 0.01	21.8	74.3	80.0	78.0	78.4
Quality of social interaction	18.4	24.9	29.4#	15.4#	0.02	21.0	77.2	60.6	76.0	80.9
Sexual function	73.9*	90.8*,‡	66.3‡	79.8	< 0.01	79.7	66.7	63.3	60.5	35.6
Sleep	59.5†	64.8	58.9	66.0†	0.02	62.3	58.1	61.2	59.9	75.5
Social support	63.5	73.8	77.1	69.5	0.17	69.0	73.0	72.0	74.1	86.7
Dialysis staff encouragement	95.7*	83.0*,§	93.2	92.1§	< 0.01	90.9	80.5	79.3	78.0	90.8
Patient satisfaction	86.3*,¶	73.5*	70.1¶	82.1	< 0.01	79.7	68.9	76.2	69.2	72.6
SF-36 component										
Physical functioning	54.1	63.5§	52.3	37.8§	< 0.01	53.1	45.0	60.3	42.7	61.0
Role physical	29.1†	35.3§	25.0	7.9†,§	< 0.01	25.9	37.2	46.5	37.6	59.0
Pain	72.9	72.8	59.4	66.8	0.18	69.8	56.4	61.4	57.1	67.4
General health	53.7†	51.0§	48.1	36.1†,§	< 0.01	48.5	36.1	40.7	41.0	59.0
Emotional well being	72.0	73.4	67.3	76.9	0.34	72.8	60.8	61.8	68.2	66.1
Role emotional	34.7*	56.0*,‡,§	31.9‡	22.0§	< 0.01	37.8	49.1	48.7	58.0	71.2
Social function	77.9†,¶	67.0	62.0¶	63.4†	< 0.01	69.7	62.2	69.2	63.5	76.6
Energy/fatigue	59.9	61.9	58.1	67.8	0.24	61.9	42.4	50.8	43.4	60.4
Overall score	55.8	59.8	55.2	54.2	0.06	56.5	62.7	63.3	63.7	62.3

KDQOL: Kidney Disease Quality of Life; SF: short form; P-HRQoL: poor health-related quality of life; SLP: Ciudad Valles, San Luis Potosi; Veracruz: Xalapa, Veracruz; Sinaloa: Culiacán, Sinaloa; Puebla: Puebla, Puebla.
ANOVA *post hoc* comparison: *Sinaloa vs. Veracruz; †Sinaloa vs. SLP; ‡Veracruz vs. Puebla; #Puebla vs. SLP; §SLP vs. Veracruz; ¶Sinaloa vs. Puebla.

was support from the dialysis team, similar to patients in Europe, the USA, and Brazil and in contrast to the results observed in Japan, where the cognitive dimension had the highest HRQoL score.

Furthermore, Brennan, et al., in their excellent systematic review of 47 studies, also investigated the association between biochemical parameters and HRQoL in patients with ESRD[10]. The authors identified 14 studies that evaluated the association between Kt/V, as a variable of dialysis adequacy, and the dimensions of the HRQoL of the SF36 questionnaire. The authors did not document a strong association between Kt/V and HRQoL (r = 0.01; 95% CI: –0.02-0.22; p = NS). With regard to anemia parameters, the authors identified 16 studies that evaluated the association between hematocrit value and the dimensions of HRQoL of the SF36 questionnaire. However, the authors did not find a strong association between hematocrit value and the dimensions of HRQoL (r = 0.1; 95% CI: 0.13-0.17). In two studies, the associations between hematocrit value and dimensions of HRQoL of the KDQOL component were evaluated, and only a weak statistically significant association (r < 0.2) was found between the hematocrit value and the satisfaction dimensions, effect of CKD, and quality of social interaction[17,18]. In contrast, the authors identified 16 studies that evaluated the associations between nutritional markers, such as serum albumin level, with dimensions of HRQoL of the SF36 questionnaire. A weak correlation (r < 0.2) was documented between albumin level and the different dimensions of the SF36 questionnaire, and a moderate correlation was found with physical function (r = 0.34), vitality (r = 0.22), and mental health (r = 0.29). Only one study documented a moderate association between serum albumin level and all dimensions of HRQoL of the KDQOL component (r = 0.3; p = 0.007)[19]. The authors found only one study that evaluated the association between parameters of bone metabolism (Ca x P product) and HRQoL, in which no association was documented between these variables[20]. However, a very important point to consider when analyzing the association between biochemical variables and the HRQoL score using a correlation coefficient is that the type of association between biochemical variables and clinical outcomes in patients with ESRD may have a "U"-shaped form instead of being linear, which could also occur with the HRQoL[21]. Based on this reasoning, using multivariate logistic regression, we performed an analysis of the association with ordinal or dichotomous statistical management of the main biochemical dialytic variables and the HRQoL. The independent risk factors associated with P-HRQoL in the analysis included the time spent on hemodialysis (OR = 1.02; 95% CI: 1.00-1.04; p = 0.02), use of a venous catheter vs. arteriovenous fistula for vascular access (OR = 3.2; 95% CI: 1.36-7.75; p = 0.01), and serum levels of albumin below 4 g/dl (OR = 3.55; 95% CI: 1.44-8.7; p < 0.01). In this type of multivariate analysis, Kt/V (Kt/V > or < 1.4) was analyzed dichotomously, and hemoglobin (Hb < 9 g/dl vs. Hb 9-11 g/dl vs. Hb > 11 g/dl), serum calcium (Ca < 8.5 mg/dl vs. Ca = 8.5-10 mg/dl vs. Ca > 10 mg/dl), and serum phosphorus levels (P < 3.5 mg/dl vs. P = 3.5-5.5 mg/dl vs. P > 5.5 mg/dl) were analyzed ordinally and were not associated with P-HRQoL in our population. In conclusion, these findings indicate that, while clinical and biochemical measurements provide important information to the physician regarding clinical outcomes, these parameters weakly correlate with HRQoL of patients with ESRD who receive hemodialysis. In this regard, the subjective evaluation that the individuals produce regarding their own quality of life plays an important role, and similar health states may correspond to different perceptions of the HRQoL.

Regarding the weaknesses of our study, one issue is the difficulty of precisely defining and measuring the quality of life as well as the lack of a universally accepted criterion for defining P-HRQoL based on the overall score of the KDQOL questionnaire. In contrast, our work is the first multicenter study to measure the HRQoL in Mexican patients with ESRD undergoing hemodialysis, in addition to studying the association between biochemical and dialytic factors and the HRQoL in a linear form and through multivariate logistic regression.

In conclusion, Mexican patients with ESRD undergoing hemodialysis have a marked decrease in their quality of life compared to the general population. Poor HRQoL was a common diagnosis, observed in up to 47.4% of our population. The most affected dimensions of the KDQOL component were work, cognition, and quality of social interaction, as well as the physical role, emotional role, and general health perception in the SF36 generic component. Factors associated with P-HRQoL included the use of a venous

catheter for vascular access, a serum albumin level < 4 g/dl, and time on hemodialysis. Based on these results, we can conclude that comprehensive treatment of patients with ESRD undergoing hemodialysis should include assessment of the HRQoL as a measure of dialysis adequacy and not be limited exclusively to measurement of clinical, dialytic, and biochemical parameters.

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Rev Inves Clin. 2016;68:203-12 ORIGINAL ARTICLE

Chronic Hepatitis C Treatment with Direct-Acting Antiviral Agents in a Real-Life Setting

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ABSTRACT

Background: In clinical trials, new oral direct-acting antiviral agent therapies have demonstrated a high sustained virological response rate in patients with hepatitis C virus infection. We aimed to analyze the efficacy and safety data from direct-acting antiviral agent interferon-free therapy in hepatitis C virus infection in a study performed in five different clinical settings in Mexico City; four private practice sites and one academic medical center in a real-world scenario. **Methods**: Eighty-one patients were treated with seven different direct-acting antiviral agent regimens, in which the end of treatment, sustained virological response at 12 weeks post-treatment, and adverse effects were evaluated. At their discretion, attending physicians selected the treatment regimens and durations. **Results**: In total, 70.4% of the patients were female and the mean age was 60.7 years; 74.1% had blood transfusion as a risk factor. The most common genotype was 1b (70.4%). The fibrosis stage was F3 or F4 in 55.5% of patients; liver cirrhosis was present in 44%. The overall end of treatment response was 98.8%, and the rate of sustained virological response was 96%, independent of the regimen. Three patients did not achieve sustained virological response; they had cirrhosis and were treatment-experienced, and two had hepatocarcinoma. Non-significant adverse effects during treatment were documented. **Conclusions:** In this real-life setting in Mexico, a rate of 96% of sustained virological response to direct-acting antiviral agents was achieved in an older population of patients with advanced fibrosis. This study provides data that may be useful in guiding health professionals and authorities in the development of health policies. (REV INVES CLIN. 2016;68:203-12)

Key words: Chronic hepatitis C. DAA. Direct-acting antiviral agent. Epidemiology. Hepatitis in Latin America. SVR. Sustained virological response.

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INTRODUCTION

In the first decade of the 21st century, the treatment of chronic hepatitis C primarily relied on the administration of pegylated interferon plus ribavirin (PegIFN/RBV)[1-3]. Strategies were implemented around this treatment to increase the prediction of patient response to therapy, thereby increasing its effectiveness[4,5]; notably, the determination of interleukin 28[6] and the concept of rapid response at week 4 and early response at week 12[7] helped predict patient responses. Sustained virological response (SVR) was reported in approximately 50% of the patients with hepatitis C virus (HCV) genotype 1 and 70% of those with genotype 2. These data were obtained from clinical trials primarily performed in the USA, Europe, and Asia and included a significant number of patients[8,9].

The treatment in these studies was difficult, requiring weekly injections of PegIFN for 24-48 weeks, with frequent clinical and biochemical adverse effects that were primarily associated with anemia, leukopenia, and thrombocytopenia and required the use of hematopoietic growth factors. These results often indicated an important deterioration in patient quality of life[10].

With the advent of new oral direct-acting antiviral agents (DAA) as part of the therapeutic armamentarium for hepatitis C, a significant change has occurred in the past five years. There have been recent reports of SVR rates greater than 90% after 12 weeks of treatment for the most frequent genotypes[11], in addition to therapeutic drugs administered orally, free of interferon, that do not convey significant side effects[12]. However, the new DAAs are expensive, and this cost has become one of the most important constraints limiting the number of patients who have access to treatment.

Well-designed, individual and national epidemiological studies and cost-benefit analyses have been performed throughout Latin America, allowing comparisons with first-world countries[13-15]. However, these studies have not resulted in treatment opportunities. The region is remarkably similar in its strengths and vulnerabilities. Uncertainties in drug registration and economic and health policies are the main factors affecting access to new treatments.

There is a need to provide guidance to health professionals and patients through the dissemination of information. Consistent with this approach, the purpose of the present work was to analyze the real-life experience gained from the use of DAAs outside of controlled clinical trials in Mexico; this study focused on patients who have had access to DAAs either through their own resources or by being insured privately. We believe that by analyzing the data related to effectiveness, compliance, and side effects we can assist health professionals, health authorities, and the pharmaceutical industry with advancing the development of a public health policy regarding DAA use in hepatitis C patients.

The primary objective of this study was to evaluate the efficacy and safety data of the DAA interferon-free therapy in HCV infection in four private medical sites and one academic medical center, all in Mexico City, in a real-world scenario.

MATERIALS AND METHODS

Study design and patients

This multicenter, case series, retrospective study reviewed prospectively collected data concerning the efficacy and safety of DAAs, with or without RBV, in patients with chronic HCV infection. The study was conducted in five different clinical settings in Mexico City; four were private practice settings, and one was an academic, tertiary care referral center. The ethics and research committees of each institution approved this observational study. Patient demographics (age, gender, and risk factors), virological, and clinical data, including medication dosage, were collected through individual health record reviews. The clinical severity of liver disease was established at baseline. The fibrosis stage was determined by non-invasive tests, such as the FibroTest or elastography (MRI/FibroScan®), and/or liver biopsy.

The patients included in this study had HCV infection, and the study sample was composed of treatment-naive patients and patients who had been previously exposed to PegIFN and RBV. Patients were classified as relapsers, partial responders, non-responders, protease inhibitor failures (PegIFN/RBV/boceprevir or telaprevir), and liver transplant recipients. Relapsers were defined as patients who had an

undetectable viral load at the end of treatment (EOT), but who did not achieve SVR. Partial responders were defined as patients who achieved a 2 log10 drop in HCV RNA by week 12, but did not achieve an EOT response. Non-responders were patients who did not achieve a 1 log10 reduction in HCV RNA by week 4 or a 2 log10 drop in HCV RNA by week 12. They were included independently of their fibrosis stage and liver disease grade.

Laboratory procedures

All of the patients had serum anti-HCV antibodies, determined by using a commercial kit (Vitros® 5600; Ortho Clinical Diagnostics, Raritan, NJ, USA), with 100% sensitivity and 99.75% specificity. When the test was positive, serum HCV RNA levels were quantified using a commercial real-time RT-PCR (Abbott RealTi*m*e HCV, Abbott m2000rt; Abbott Molecular Inc., Des Plaines IL, USA), with a lower limit of quantification of 12 IU/ml. The HCV genotype and subtype were determined using a commercial kit (Abbott RealTi*m*e HCV Genotype II, Abbott m2000rt; Abbott Molecular Inc., Des Plaines IL, USA).

Laboratory tests, including liver function tests, red blood cell counts, white blood cell counts, and platelet counts, were monitored at baseline; at weeks 4, 12, and 24, as needed; and 12 weeks after the completion of treatment.

Study endpoints and treatment

The study endpoints were as follows: (i) the number of patients who achieved undetectable HCV RNA at the EOT, at 12 or 24 weeks; and (ii) the number of patients who achieved SVR 12 weeks after completing treatment (SVR12).

Treatment

The DAA treatment regimens and their durations (i.e. 12 or 24 weeks) were selected at the discretion of the treating physicians. Treatment regimens included combinations of sofosbuvir (SOF), ribavirin (RBV), simeprevir (SMV), ledipasvir (LDV), ombitasvir (OBV), paritaprevir (PTV), ritonavir (r), and dasabuvir (DSV). Seventy-three patients received 12 weeks of treatment; one patient with genotype GT2 received 16 weeks of SOF/RBV. Seven patients were treated with 24-week regimens: two patients with SOF/SMV, one with SOF/RBV, two with SOF/LDV, one with SOF/LDV/RBV, and one patient with OBV/PTV/r/DSV (Table 1).

Data on adverse side effects were collected for all patients during the entire treatment and follow-up periods. These data were reviewed to identify the causal relationship with the treatment regimens.

Statistical analysis

Continuous data are expressed by the mean values and standard deviation (SD); categorical variables are expressed as absolute and relative numbers and percentages. Categorical data were analyzed with the X^2 test, and an EPI value of ≤ 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

This study included 81 patients, 57 women (70.4%) and 24 men (29.6%). The age range was 41-81 years (mean age, 60.7 years). The most common risk factor was blood transfusion, reported in 60 patients (74.1%); three patients had a history of surgery without blood transfusion (3.7%); two were healthcare workers (2.5%), and one had a family member with hepatitis C (1.2%). In 15 patients (18.5%) we were unable to determine a risk factor. Co-morbidity was present in 32 patients (39.5%); diabetes mellitus and arterial hypertension were the most frequent (seven patients with each co-morbidity), followed by a history of cancer in five patients. Digestive, thyroid, and ocular diseases were present in three patients each, and dyslipidemia was present in two patients. Cardiovascular, rheumatologic, and cerebrovascular diseases were present in one patient each.

The most common HCV genotype was type 1, identified in 73 patients (90.1%); 16 patients (19.8%) had subtype 1a (GT1a), and 57 (70.4%) had subtype 1b (GT1b). Genotype 2 (GT2) was identified in seven patients (8.6%), and one patient (1.2%) had genotype 3 (GT3). In 71 patients (87.7%), the HCV RNA viral load was ≤ 6,000,000 IU/ml, and in 10 patients (12.3%) the viral load was > 6,000,000 IU/ml.

Table 1. Direct-acting antiviral regimens selected by the physicians to treat patients with chronic hepatitis C

DAA treatment regimens	Number of patients (n = 81)
SOF 400 mg QD/SMV 150 mg QD 12 weeks	11
SOF 400 mg QD/SMV 150 mg QD 24 weeks	2
SOF 400 mg QD/SMV 150 mg QD/RBV* 12 weeks	1
SOF 400 mg QD/RBV* 12 weeks	4
SOF 400 mg QD/RBV* 16 weeks	1
SOF 400 mg QD/RBV* 24 weeks	1
SOF 400 mg QD/LDV 90 mg QD 12 weeks	22
SOF 400 mg QD/LDV 90 mg QD 24 weeks	2
SOF 400 mg QD/LDV 90 mg QD/RBV* 12 weeks	6
SOF 400 mg QD/LDV 90 mg QD/RBV* 24 weeks	1
OBV/PTV/r (25/150/100 mg QD)/DSV (250 mg BID) 12 weeks	13
OBV/PTV/r (25/150/100 mg QD)/DSV (250 mg BID) 24 weeks	1
OBV/PTV/r (25/150/100 mg QD)/DSV (250 mg BID)/RBV* 12 weeks	16

*The ribavirin dose ranged between 800 and 1,200 mg.
BID: twice daily; DAA: direct-acting antiviral agent; DSV: dasabuvir; LDV: ledipasvir; OBV: ombitasvir; PTV: paritaprevir; QD: once daily; r: ritonavir; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir.

Table 2. Baseline characteristics of patients with chronic hepatitis C

Patient characteristics	Number of patients (%) (n = 81)
Age (years)	
Mean age	60.77
Range	41-81
Gender	
Female	57 (70.4)
Male	24 (29.6)
HCV genotype	
1	2 (2.5)
1a	14 (17.3)
1b	57 (70.4)
2	7 (8.6)
3	1 (1.2)
Fibrosis stage	
F0	11 (13.6)
F1	17 (21.0)
F2	8 (9.9)
F3	9 (11.1)
F4	36 (44.4)
Child-Pugh class	
A	32 (88.8)
B	2 (5.6)
C	2 (5.6)
Treatment-naive	40 (49.4)
Treatment-experienced	41 (50.6)

HCV: hepatitis C virus.

Eleven patients (13.6%) underwent liver biopsy; five of them also had a non-invasive test done, and in all cases there was a correlation between both tests. In 86.4% of patients, fibrosis stage was determined by a non-invasive test: FibroScan in 12 patients; FibroTest in 13; magnetic resonance imaging in 16; abdominal ultrasound and clinical and laboratory findings in 42 patients. Regarding the fibrosis stage, the distribution in the study sample was as follows: F0 = 11 (13.6%), F1 = 17 (21%), F2 = 8 (9.9%), F3 = 9 (11.1%), and F4 = 36 (44.4%). Patients in stage F4 were further classified as Child A (88.8%), Child B (5.6%), or Child C (5.6%) (Table 2).

Of the 81 patients, 40 (49.4%) were treatment-naive, and 41 (50.6%) had been previously treated with PegIFN/RBV; five of these patients had also been treated with PegIFN/RBV/boceprevir; one patient had been treated with PegIFN/RBV/telaprevir, and one patient had received PegIFN/RBV/SMV. Of the previously treated patients, 18 (43.9%) were non-responders, 18 (43.9%) were relapsers, one (2.44%) had a partial response, and four patients (9.75%) had a history of discontinuing previous treatments because of adverse effects. Four patients (4.9%) had hepatocellular carcinoma (HCC), three had undergone liver transplantation (3.7%), and one patient (1.2%) had HIV.

Efficacy

An EOT response occurred in 80 of the 81 patients (98.8%), independent of the treatment regimen. So far, 75 patients have completed the time framework to evaluate response to treatment at 12 weeks after completing treatment (SVR12). The SVR12 rate was 96% (72/75 patients).

Table 3. Rates of sustained virological response at 12 weeks according to genotype, fibrosis stage, and prior treatment history

	EOT No. (%) (n = 81)	SVR12 No. (%) (n = 75)
	80/81 (98.8)	72/75 (96.0)
HCV genotype		
1a	15/16 (93.8)	14/16 (87.5)
1b	57/57 (100)	51/51 (100)
2	7/7 (100)	6/7 (85.7)
3	1/1 (100)	1/1 (100)
Fibrosis stage		
F0	11/11 (100)	11/11 (100)
F1	17/17 (100)	14/14 (100)
F2	8/8 (100)	7/7 (100)
F3	9/9 (100)	8/8 (100)
F4	35/36 (97.2)	32/35 (91.4)
Previous treatment	EOT 40/41 (97.5)	SVR12 35/38 (92.1)
Non-responders	17/18 (94.4)	17/18 (94.4)
Relapsers	18/18 (100)	13/15 (86.6)
Partial responders	1/1 (100)	1/1 (100)
IFN intolerant	4/4 (100)	4/4 (100)

EOT: end of treatment; IFN: interferon; SVR12: sustained virological response at week 12 of treatment.

According to genotype, the EOT response was 93.8% for GT1a, 100% for GT1b, 100% for GT2, and 100% for GT3. Considering the fibrosis stage, the EOT response was 100% in the F0, F1, F2, and F3 patients and 97.2% in the F4 patients.

The SVR12 rate was achieved in 87.5, 100, 85.7, and 100% of the patients with GT1a, GT1b, GT2, and GT3, respectively. The SVR12 rate was 100% in the patients with fibrosis stages F0, F1, F2, and F3. Patients in stage F4 achieved a lower SVR12 rate of 91.4%.

An EOT response was achieved in 97.5% of the patients previously exposed to PegIFN/RBV-based treatments. The response rate in the previous non-responders was 94.4%. In the relapsers, partial responders, and PegIFN/RBV intolerant patients the EOT responses were 100%. An SVR12 was achieved in 92.1% of the treatment-experienced patients. In the previous non-responders, the SVR12 rate was 94.4%; the rates were 86.6% in the previous relapsers and 100% in the partial responders and PegIFN/RBV intolerant patients (Table 3). The EOT response and SVR12 in naive patients were 100%.

According to the duration of therapies, the two patients that relapsed received 12-week regimens with SOF/SMV/RBV and SOF/RBV, and one non-responder patient was treated with OBV/PTV/r/DSV for 24 weeks.

Three patients (4%) did not achieve SVR12: one patient was a non-responder, and two patients relapsed (Table 4). The patient who failed to achieve an EOT response was a 70-year-old woman with cirrhosis, classified as Child A, who was a previous non-responder to PegIFN/RBV. The patient had GT1a and was treated with OBV/PTV/r/DSV, without RBV, for 24 weeks.

The two relapsers had cirrhosis, classified as Child A, and had relapsed from previous treatment, one from PegIFN/RBV and one from PegIFN/RBV/SMV; both patients had been diagnosed with liver cancer and were treated before receiving the DAA treatment. One patient was a 75-year-old woman with GT1a, with HCC classified as early stage (A) according to the Barcelona Clinic Liver Cancer (BCLC) staging system; she received radiofrequency ablation with no evidence of tumor during surveillance. She was treated with SOF/SMV/RBV for 12 weeks. The other patient was a 58-year-old man with GT2, who had HCC classified as BCLC intermediate stage (B), who had received transarterial chemoembolization and had no evidence of tumor when he was treated with SOF/RBV for 12 weeks. A total of four patients had a history of HCC: the two patients

Table 4. Rates of end of treatment and sustained virological response at week 12 of treatment according to direct-acting antiviral treatment regimens

	EOT (n = 81) No. (%)	SVR12 (n = 72) No. (%)	Non-responder (n = 1) No. (%)	Relapse (n = 2) No. (%)
SOF/SMV n = 13	13 (100)	13 (100)	0	0
SOF/SMV/RBV n = 1	1 (100)	0 (0)		1 (100)
SOF/RBV n = 6	6 (100)	5 (83.3)	0	1 (16.7)
SOF/LDV n = 24	24 (100)	22 (100)	0	0
SOF/LDV/RBV n = 7	7 (100)	7 (100)	0	0
OBV/PTV/r/DSV n = 14	13 (92.9)	11 (91.6)	1 (8.4)	0
OBV/PTV/r/DSV/RBV n = 16	16 (100)	14 (100)	0	0
Total n = 81	80 (98.8)	72 (96)	1 (1.4)	2 (2.6)

DAA: direct-acting antiviral; DSV: dasabuvir; EOT: end of treatment; LDV: ledipasvir; OBV: ombitasvir; PTV: paritaprevir; r: ritonavir; RBV; ribavirin; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained virological response at week 12 of treatment.

referred to previously who did not achieve SVR12, and a 61-year-old woman, GT1b, naive to previous treatment, with F4 fibrosis stage and an HCC in early stage (A) who underwent surgical resection, with no evidence of tumor; she received SOF/SMV for 12 weeks and achieved SVR12. The other patient was a 62-year-old man, GT1b, naive to previous treatment, fibrosis stage F4, with HCC in early stage (A), who underwent radiofrequency ablation, with no evidence of tumor while being treated with SOF/SMV for 12 weeks, and who also achieved SVR12.

Three patients received treatment post-liver transplantation, all of whom achieved SVR12. Two of these patients (GT1b) received SOF/SMV for 12 weeks and SOF/LDV/RBV for 12 weeks, and one patient (GT2) was treated with SOF/RBV for 24 weeks.

Safety

Of the 81 patients, 35.8% experienced an adverse event. The events were minor in all of the patients, and none of them discontinued their treatment. The most common adverse events were asthenia in 12.3% of the patients, and headache in 6.2%, followed by pruritus, diarrhea, and malaise, which were each present in 3.7% of the patients. Less frequently occurring adverse events were rash, myalgia, and insomnia. Anemia occurred in six patients (8.6%), and it was the most common adverse event in patients receiving RBV. In two patients the RBV dose was modified but not suspended. No patient discontinued the treatment because of anemia or received erythropoietin or transfusion. According to the regimen received, the adverse effects occurred more frequently in patients treated with OBV/PTV/r/DSV or OBV/PTV/r/DSV/RBV at rates of 8.6 and 11.1%, respectively, followed by SOF/LDV or SOF/LDV/RBV, both at 3.7%. A total of 4.9% of the patients treated with SOF/SMV experienced adverse events; the adverse event rate was 2.4% for SOF/RBV, and no adverse events were reported in patients treated with SOF/SMV/RBV (Table 5).

Based on these results, we are proposing a decision-making algorithm for evaluation and treatment with DAA agents that can be applied independently of the selected treatment scheme (Fig. 1).

DISCUSSION

The effectiveness of DAAs as therapeutic agents for hepatitis C has been clearly demonstrated worldwide[16,17]. The present study aimed to evaluate the overall effect of DAAs on chronic hepatitis C and was

Table 5. Adverse events associated with direct acting antiviral treatment in patients with chronic hepatitis C

Adverse event	No. (%)
Any adverse event	29 (35.8)
Any adverse event leading to discontinuation	0
Any serious adverse event	0
Common adverse events	
Asthenia	10 (12.3)
Headache	5 (6.2)
Pruritus	3 (3.7)
Diarrhea	3 (3.7)
Malaise	2 (2.5)
Rash	2 (2.5)
Insomnia	2 (2.5)
Myalgia	1 (1.2)
Insomnia	1 (1.2)
Anemia	7 (8.6)
Thrombocytopenia	1 (1.2)
Leukopenia	1 (1.2)

not designed as a comparative study of different treatment regimens.

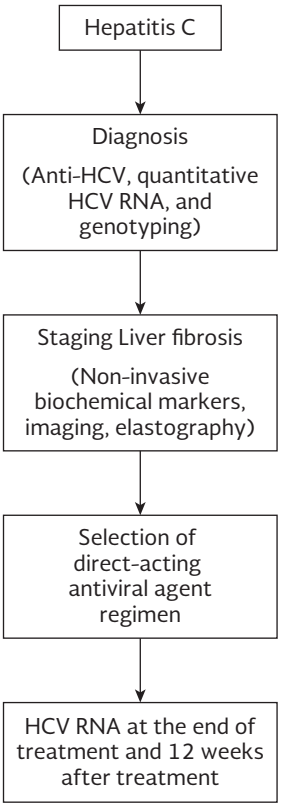
As the registration of DAAs in Mexico has become a reality[18], the only patients who have thus far benefited from these new forms of therapy are those with private insurance or the economic means to obtain the medication.

Herein, we analyzed the data obtained in this group of individuals with the purpose of contributing to the process of making these drugs available to the general public, who represent the vast majority of chronic HCV patients in the country, where only 0.44% of the population has private insurance[19]. Overall, this analysis may be helpful in determining soon who should be treated and when, in a scenario where prioritization is necessary.

This study represents real-life experiences and is not a large-scale HCV therapy controlled trial, which allows the identification of relevant issues that are specific to the region and that represent hurdles in accessing treatment.

Patients with genotypes 1, 2, or 3 were included, with GT1b being the most frequent. These results are similar to the findings previously reported in Mexico[20,21] and in other regions in Latin America[22,23]. Most novel DAAs are now recognized to induce a good response

Figure 1. Decision-making algorithm for hepatitis C evaluation and treatment with direct-acting antiviral agents.



in patients infected with GT1a and GT1b HCV, including those with compensated cirrhosis.

The mean age of the study population was 60.7 years. Among those patients who had received a transfusion, the length of exposure to the virus was 43.6 years. Not surprisingly, 55.5% of the patients had an F3 or F4 fibrosis stage, 36/81 (44.4%) had liver cirrhosis, three had undergone liver transplantation, and four had HCC. These data align with results from a previous report by our group using the FibroTest to identify the stage of liver fibrosis in 261 HCV-infected patients. In that study, stages F3 and F4 represented 55% of the sample[24].

In 1989, cirrhosis associated with hepatitis C accounted for only 5% of all cases in western countries; that rate increased to 10% in 1998 and 20% in 2006 as the age and duration of illness of those infected began to increase. The proportion of patients with cirrhosis was projected to reach 24.8% by 2010, 37.2% by 2020, and 44.9% by 2030[25]. Data from the present study indicate that the patients in our country are

late to receive the new DAA therapy. In addition, these patients are older, which validates the fact that fibrosis progression is in general inversely related to age, and explains why cirrhosis and its complications occur most commonly after 60 years of age.

Fibrosis staging has become a relevant issue in determining how to optimize hepatitis C treatment; clearly, the best strategy involves treating all patients (F0-F4), independently of the degree of fibrosis. Providing treatment at earlier stages will reduce the number of patients that develop more severe liver disease and will reduce the cost of care of the complications of advanced fibrosis and cirrhosis. However, giving treatment at stages F3-F4 implies treating those patients at a greater risk of developing complications in the near future, such as esophageal variceal bleeding, encephalopathy, and HCC. Furthermore, in F3-F4 patients achieving SVR, a significant decrease in morbidity and mortality related to liver disease has been demonstrated[26,27].

At present, no single policy regarding treatment for hepatitis C can be applied worldwide, and each region and country will need to adjust to their own situations. In particular in Latin America, funding and medical resources do not presently allow for a strategy in which all patients with hepatitis C can access DAA treatment. Interestingly, a recent report on how to optimize HCV treatment in resource-constrained countries (including Egypt, Thailand, and Ivory Coast) demonstrated that prioritizing treatment in patients in stages F3 and F4 is the most effective strategy in terms of life-years saved (i.e. 13.1-22.0% in the next 5-10 years)[28]. Any strategy is better than the alternative of continuing with the current treatment levels in which cases of advanced liver disease and liver-related deaths will continue to increase through 2030[29].

Treatment-experienced patients represented the most prevalent group (50.6%) in our study, including previous null responders, relapsers, partial responders, and patients who had interrupted previous IFN-based treatment because of significant side effects; the remaining 49.4% of participants were treatment-naive. The overall EOT response was 98.8%, and the SVR12 was 96%. Ten patients had a viral load > 6,000,000 UI/ml, all of whom responded to treatment independently of the regimen. This population represents 12% of our sample, which is greater than values previously reported in the literature[30] and may be related to the higher percentage of cirrhotic patients in our sample. Adverse events occurred in 35.8% of the patients; all the events were mild and did not affect their treatment compliance. These events occurred in 11.1% of patients receiving the OBV/PTV/r/DSV+RBV regimen and in 3.7% of patients receiving the SOF/LDV+RBV regimen.

The three patients who failed to achieve SVR had advanced fibrosis; two were older than 75 years, two had GT1a and one had GT2, and two had HCC. They were all experienced patients, including two relapsers and one non-responder.

The American Association for the Study of Liver Diseases (AASLD) 2015 guidelines recommend treatment in patients with HCC, regardless of whether they are candidates for liver transplantation. Our results show a low SVR12 in this group of patients because only 2/4 (50%) patients achieved SVR12, and none of those patients presented with decompensated liver function.

Based on these results, one can speculate that if the viremic population in Mexico is approximately 0.7%, there are about 355,000 patients in stages F3-F4 who would be candidates to receive DAAs in the public sector. This finding imposes an important health burden in terms of morbidity and mortality[31].

Contrary to the design of clinical trials, our real-life sample shows that 39.5% of the patients had an associated comorbidity, which may imply the need for additional medications independent of their health hazard risk. This finding becomes a relevant issue because one of the main factors that determine the percentage of SVR is the concomitant use of medications. These patients should be monitored at more frequent intervals than HCV patients without health conditions that promote liver injury[32]. If DAAs are to be approved for generalized use in the public and private sectors, the implementation of a solid system is necessary to identify and guide practitioners in the knowledge of drug-drug interactions to prevent adverse events and treatment failure[33].

Because most of the patients in Mexico and Latin America are as yet unaware of their disease[15] it is necessary to increase the level of education and awareness

among individuals at risk and in the medical community. There is a need to increase the diagnostic and service delivery capacities for HCV infection. Simultaneously, a new screening policy in addition to screening blood bank products must be implemented to allow earlier detection of patients and to identify the highest priority groups for prevention and treatment towards eradication. With such high SVR percentages, developed countries can voice concerns about eradication; however, eradication is not yet the case in the Latin American region where detection is still an important problem and testing policies are urgently needed. A significant caveat is that screening should be attached to access to treatment. Even in more advanced countries, no action has been taken in 30% of patients who tested positive for HCV[34], and only approximately 15% of the patients diagnosed with chronic HCV infection have actually received treatment[35].

Latin American countries must develop courageous, successful, and long-term planning policies that should lead to significant medical advances in the region, aligning them with the global preventive and therapeutic strategies being developed in other regions of the world. Real-world data can help guide health professionals and policy makers[36,37]. Undoubtedly, a national action plan accompanied by federal guidelines for the screening and treatment of hepatitis C should be advocated.

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PERMANYER

Rev Inves Clin. 2016;68:213-8 ORIGINAL ARTICLE

IKAROS Gene Deleted B-Cell Acute Lymphoblastic Leukemia in Mexican Mestizos: Observations in Seven Patients and a Short Review of the Literature

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ABSTRACT

Background: In B-cell acute lymphoblastic leukemia, one of the most frequent cytogenetic alterations is the presence of the Philadelphia chromosome. Recently, newly identified genetic alterations have been studied, among them the *IKZF1* deletion. *IKZF1* encodes IKAROS, a zinc finger protein that plays an important role in hematopoiesis involving the regulation process of adhesion, cellular migration, and as a tumor suppressor. **Objective:** We aimed to study the impact of *IKAROS* deletion in the evolution and prognosis of B-cell acute lymphoblastic leukemia. **Materials and Methods:** At a single center we prospectively studied patients diagnosed with B-cell acute lymphoblastic leukemia and screened for *IKZF1* deletion using the multiplex ligation-dependent probe amplification method. We did a descriptive analysis of patients positive for the *IKZF1* deletion to determine its impact on the evolution of the disease and survival rate. **Results:** Between 2010 and 2015, 16 Mexican mestizo patients with B-cell acute lymphoblastic leukemia were prospectively screened for *IKZF1* deletion; seven (43%) were positive and were included for further analysis. The age range of patients was 13-60 years; six were males and one female. All cases had type B acute lymphoblastic leukemia. Of the seven patients, two died, three were lost to follow-up, and two continue in complete remission with treatment. Results are worse than those in a group of patients with non-mutated *IKAROS* B-cell acute lymphoblastic leukemia previously studied in our center. **Conclusions:** Although this is a small sample, the presence of *IKAROS* deletion in acute lymphoblastic leukemia patients could represent a poor-prognosis marker and was probably related to therapy failure. It is also possible that this variant of leukemia may be more prevalent in Mexico. More studies are needed to define the role of *IKZF1* deletion in acute lymphoblastic leukemia and the real prevalence of the disease in different populations. (REV INVES CLIN. 2015;68:213-8)

Key words: B-cell acute lymphoblastic leukemia. IKAROS. IKZF1.

INTRODUCTION

B-cell acute lymphoblastic leukemia (ALL) is a hematological malignant disorder characterized by clonal proliferation and tissue infiltration with lymphoid progenitor cells that can be presented in both children and adults[1,2]. The incidence of ALL decreases with age and represents 30% of all childhood cancers and 6% of all cancers in teenagers[3,4]. In almost all patients with B-cell ALL, structural chromosomal changes, such as translocations,

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inversions, and deletions, can be found[2]. One of the most common cytogenetic abnormalities in adults with ALL is the Philadelphia chromosome, representing 20-30% of all cases[5]. The fusion of *ABL1* gene in chromosome 9 to the *BCR* gene on region q11 in chromosome 22 results in the BCR-ABL tyrosine kinase activation and acts as an oncogene for ALL[6].

There is also a rare deletion in the *IKAROS* (*IKZF1*) gene involved in ALL that may increase the risk of relapse in this type of disease[6]. This gene regulates lymphocyte differentiation, is restricted to the fetal and adult hemo-lymphopoietic system, and is localized on 7p12.2[7]. *IKAROS* is involved in the process of multipotential hematopoietic stem cell differentiation into the three major hematopoietic lineages: erythroid, myeloid, and lymphoid[7]. The *IKAROS* dysfunction is linked to hematologic malignancies; loss of *IKAROS* activity would decrease the numbers of differentiating erythroid cells[8]. The loss of activity in *IKZF1* is determined by molecular mechanisms: deletions, intragenic deletions, or loss of the entire *IKZF1* gene[9].

Although *IKAROS* may function as a tumor suppressor gene, the exact mechanism for this activity remains unknown. However, this characteristic is related to target genes that improve different mechanisms such as a positive regulation in the B-cell and T-cell differentiation, downregulation of the Notch signaling pathway, negative regulation of cellular proliferation (that is given by c-Myc oncogene repression by *IKAROS* activation of p27 and downregulation of cyclin D3), and regulation of apoptosis (*IKAROS* may regulate Bcl-xL expression)[10-14]. The function of *IKAROS* may be regulated by ubiquitination, sumoylation, and phosphorylation[15].

The aim of this study was to conduct a descriptive analysis of patients with *IKZF1* deletion and to correlate this cytogenetic abnormality with the evolution of the disease and survival rate.

MATERIALS AND METHODS

We conducted a prospective study of patients diagnosed with B-cell ALL at a single center and screened for *IKZF1* deletion using multiplex ligation-dependent probe amplification (MLPA) method. Other translocations such as t(12;21), t(9;22)BCR-ABL, and t(1;19) were also screened for. MLPA is a multiplex PCR assay that identifies variations in the copy number of human genes using up to 40 probes specific for a different DNA sequence and is employed for the molecular diagnosis of genetic diseases. MLPA reaction involves five steps: (i) DNA denaturation and probes hybridization, (ii) ligation reaction, (iii) PCR amplification, (iv) separation of amplification products by electrophoresis, and (v) data analysis[16].

In the patients positive for *IKZF1*, different variables were analyzed: white blood cell (WBC) count at diagnosis, type of treatment, survival, and relapse. The variables were analyzed to make a descriptive study and correlate them with the impact of *IKAROS* on the evolution of the disease and the survival rate of the patients studied.

RESULTS

A total of 16 consecutive patients with ALL studied after 2010 were prospectively screened for the *IKZF1* deletions and seven (43%) were found to be positive. The descriptive analysis was focused on the latter patients. The age range of patients was 13-60 years; six were male and one female. The ALL type was B in all cases. Regarding the presence of other translocations, all patients were negative for t(12;21) and t(1;19), and only one was positive for t(9;22)BCR-ABL. In one patient, del(1)(q32), t(5;15), (q31;q22) was also found. Table 1 depicts patient characteristics and translocations. Analysis of the WBC count at diagnosis showed that five patients had leukocytosis and two, leukopenia. The treatment used was a modification of St. Jude Total Therapy XI[17], which consists of a combination of systemic chemotherapy and central nervous system-directed therapy. Currently, only two patients continue with the treatment; two patients achieved remission, two had relapse, three were lost to follow-up, and two have died. One patient was given dasatinib 50 mg/day in addition to the chemotherapy. Figure 1 shows the overall survival of the *IKAROS*-positive (n = 7) versus *IKAROS*-negative (n = 9) patients with B-cell ALL studied.

DISCUSSION

B-cell ALL is linked to dysfunctional IKAROS proteins; *IKAROS* is a key regulator to the homeostasis, development, and proliferation of normal lymphoid cells[18,19].

Table 1. Salient features of patients with deleted *IKZF1*

Patient	Age at diagnosis (years)	Diagnosis	*IKZF1*	White blood cell count at diagnosis	Other genetic alterations	Treatment	Relapse during treatment	Survival status
1	23	B-ALL	+	1.2	Chromosome 7 aneuploidy t(9;22) BCR-ABL	Chemotherapy	-	Lost at 334 days
2	18	B-ALL	+	21.3	del (1)(q32), t(5;15),(q31;q22), dup(6)(p12p25) add(17)(q22), t(7;15)(p15;q11.2)	Chemotherapy	+	Lost at 236 days
3	52	B-ALL	+	151.6	None	Chemotherapy	-	Lost at 55 days
4	23	B-ALL	+	1.9	None	HSCT	+ 11 months after treatment	Dead after 365 days
5	13	B-ALL	+	67.0	MLL gene (4 cell +)	Chemotherapy + dasatinib 50 mg/day	-	In treatment 243 days
6	58	B-ALL	+	94.4	MLL gene (7 cell +)	Allogeneic HSCT	-	Dead after 171 days
7	59	B-ALL	+	164.0	None	Chemotherapy	-	In treatment 38 days

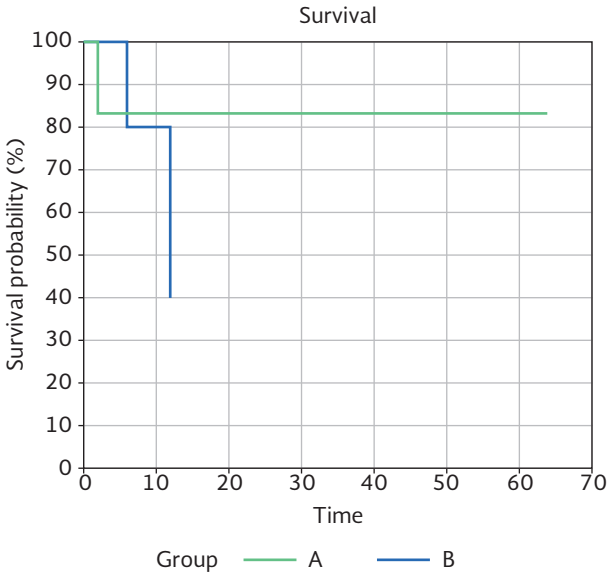
B-ALL: B-cell acute lymphoblastic leukemia; HSCT: hematopoietic stem cell transplantation.

In hematopoietic stem cells (HSC) some transcription factors mediate gene expression[20]. The *IKAROS* gene encodes a novel zinc finger with N-terminal DNA-binding protein and dimerization domains in C-terminal; it confers the *IKAROS* gene the ability to play an important role in the regulation of the lymphoid lineages development[7,20], particularly in hematopoiesis (stem cells, T and B lymphocytes, dendritic cells, natural killer cells)[21,22]. Both regions, N-terminal and C-terminal, have sub-regions that compound zinc fingers: the N-terminal has four amino terminal zinc fingers that regulate their binding to DNA; C-terminal has two zinc fingers that mediate the interaction with other type of IKAROS proteins (Fig. 2); an alternative splicing after transcription is involved in the creation of isoforms. These isoforms conserve in their structure the exons one and two, although in the end the total number of exons varies[7,21,23]. There are 11 isoforms as a result of the alternative splicing from which only IK-1, IK-2, IK-3, and IKX are functional, in fact, for their capacity to bind to DNA. IK-1 and IK-2 are localized in the nucleus, regulating lymphocyte differentiation, being the most important transcriptional factors in this process. In thymocytes, the presence of IK-4 is abundant, and IK-3, IK-5, and IK-6 are in smaller amounts. IK-5, IK-6, IK-7, and IK-8 have a poor activity to bind DNA, and are considered as dominant-negative[21-24].

IKAROS protein zinc finger is involved in the regulation of the process of adhesion and cellular migration; this process begins with the activation of genes and chemokine receptors controlling the adhesion and migration of pro-B-cells[25]. IKAROS plays an important role in hematopoiesis, as stated previously, mainly through the relationship between IKAROS and the nucleosome remodeling and deacetylase (NuRD) complex, which controls chromatin organization. IKAROS, CDK9, and the NuRD subunit Mi2 are factors that perform an important function during transcription elongation; studies demonstrate that the NuRD complex helps polymerase II progression during transcription elongation[26].

An alteration in *IKZF1* may change the proliferation process in lymphoid cells, and is linked to a poor

Figure 1. Overall survival of acute lymphoblastic leukemia patients with the *IKAROS* deletion (Group B) versus *IKAROS* non-deleted (Group A).



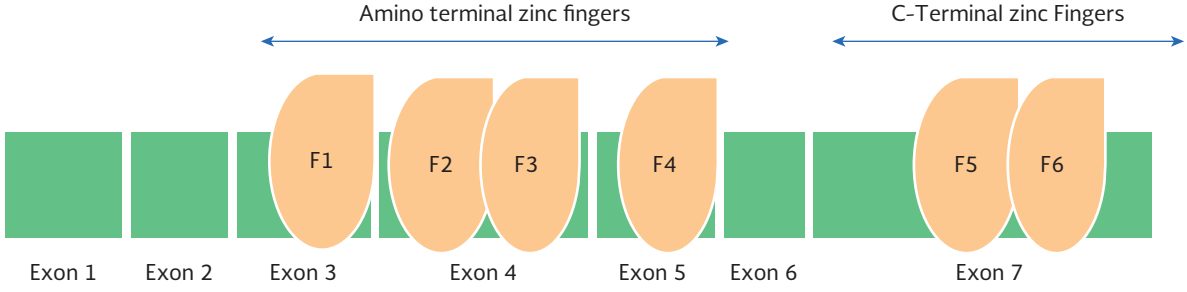
relapse-free survival in adult ALL. These changes in *IKZF1* expression are key to understanding and stratifying a therapeutic plan[27]. Other abnormalities that may modify the outcome and the therapy are the cytogenetic alterations, with the Philadelphia chromosome (Ph) being the worst prognostic factor[28]. The Ph chromosomal abnormality was the first one described in association with chronic myeloid leukemia (CML) and linked with malignant disease. It is the most characteristic structural chromosome alteration in CML, observed in 95% of these patients and in 15-30% of adults with ALL. Ph-positive ALL is related to a poor outcome in adults and in children, with a shorter remission and shorter survival. According to the literature, patients with Ph-positive ALL are older and can achieve complete remission with induction chemotherapy[29]. In this study, in only one patient we found a *IKZF1* deletion with Ph-positive with aneuploidy, but this patient was lost to follow-up. Chromosome gains or losses are not rare in ALL, although their incidence is higher in myeloid leukemias, the most observed abnormalities being the trisomy or monosomy[1].

In a group of 221 patients, Mullighan, et al.[30] found the *IKZF1* gene factor affected in 15% of B-cell ALL patients, and mutations of *IKZF1* were found in 70-80% of Ph-positive B-cell ALL, which the authors related with a poor outcome[15,30]. These data contrast with what we have observed in our study, in which 7/16 patients with B-cell ALL had a mutated form of *IKAROS*. Despite the low number of patients in our study, we can speculate that *IKAROS*-positive ALL may be more frequent in Mexico than in other populations.

The induction of complete remission and the event-free survival may be predicted by the leukocyte count: hyperleukocytosis (> 100 x 10^9/l) is associated with an increased risk of therapy failure[31]. Only two of our patients had hyperleukocytosis; one was lost to follow-up and the other patient is currently under treatment with chemotherapy. Although one patient had leukopenia, he relapsed and died.

The chemotherapy regimen used in all of our patients was a modification of the St. Jude Total Therapy XI. Although this therapy was originally employed for children, we have used it in adults with a favorable response[32]. Recent information suggests that patients with the *IKAROS* deletion and BCR-ABL-positive

Figure 2. Exon composition of *IKAROS*. The first four zinc fingers, which conform the N-terminal DNA binding domain and C-terminal, conformed by two zinc fingers that are in charge of the interactions with other types of *IKAROS*.



ALL may improve their prognosis by using tyrosine kinase inhibitors (TKI) during the maintenance therapy. We have employed dasatinib in one of the patients who is the one with the longest survival, both overall and relapse-free. It may be possible that ALL patients with the *IKAROS* deletion could benefit from the treatment with TKIs[6].

According to the literature, hematopoietic stem cell transplantation (HSCT) may cure some patients, even if the transplant is performed during the first remission or after relapse, showing a similar response and disease-free survival two years after the procedure[33]. In our group of patients, two were given an allogeneic HSCT; one of them relapsed and was treated with further chemotherapy for one year before his death, whereas the other patient was treated for six months and subsequently relapsed and died.

Although this is a study from a small sample, it could suggest that *IKAROS* gene deletion is an aggressive marker similar to BCR-ABL and that this deletion may be more frequent in Mexican mestizos. Larger studies are needed to define the role of the *IKZF1* deletion in B-cell ALL and its prevalence in different populations.

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