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Original Article

Patient Survival and Safety With Biologic Therapy. Results of the Mexican National Registry Biobadamex 1.0☆

Lucio Ventura-Ríos,[a] David Bañuelos-Ramírez,[b] María del Carmen Hernández-Quiroz,[c] Manuel Robles-San Román,[d] Fedra Irazoque-Palazuelos,[e] María Victoria Goycochea-Robles[f,*]

[a] *Consulta de Reumatología, Hospital Central Sur PEMEX, México DF, Mexico*
[b] *Consulta de Reumatología, Hospital Manuel Avila Camacho IMSS, Puebla, Mexico*
[c] *Departamento de Reumatología, Hospital Especialidades Centro Médico La Raza IMSS, México DF, Mexico*
[d] *Consulta de Reumatología, Centro Médico Toluca, Toluca, Estado de México, Mexico*
[e] *Departamento de Reumatología, Centro Médico Nacional 20 de Noviembre ISSSTE, México DF, Mexico*
[f] *Unidad de Investigación en Epidemiología Clínica, Hospital Regional N.° 1 IMSS, México DF, Mexico; Unidad de Investigación Colegio Mexicano de Reumatología, México DF, Mexico*

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ABSTRACT

This work reports patient treatment survival and adverse events related to Biologic Therapy (BT), identified by a multicenter ambispective registry of 2047 rheumatic patients undergoing BT and including a control group of Rheumatoid Arthritis (RA) patients not using BT. The most common diagnoses were: RA 79.09%, Ankylosing Spondilytis 7.96%, Psoriatic Arthritis 4.40%, Systemic Lupus Erythematosus 3.37%, Juvenile Idiopathic Arthritis 1.17%. A secondary analysis included 1514 cases from the total sample and was performed calculating an incidence rate of any adverse events of 178×1000/BT patients per year vs 1009×1000/control group patients per year with a 1.6 RR (95% CI 1.4–1.9). For serious adverse events the RR was: 15.4 (95% CI 3.7–63.0, *P*<.0001). Global BT survival was 80% at 12 months, 61% at 24 months, 52% at 36 months and 45% at 48 months and SMR: 0.23 (95% CI 0.0–49.0) for BT vs 0.00 (95% CI 0.0–0.2) for the control group. In conclusion, BT was associated to a higher infection risk and adverse events, compared to other patients. Mortality using BT was not higher than expected for general population with same gender and age.

Terapia biológica: sobrevida y seguridad en padecimientos reumáticos. Resultados del Registro Nacional Biobadamex 1.0

Palabras clave:
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RESUMEN

Mediante registro multicéntrico ambispectivo de 2.047 pacientes con diversas afecciones reumáticas bajo terapia biológica (TxB), incluyendo un grupo control de pacientes con artritis reumatoide (AR) sin TxB, se reporta la supervivencia en la terapia y eventos adversos asociados a su uso. Los diagnósticos más frecuentes son: AR 79,09%; espondilitis anquilosante (EA) 7,96%; artritis psoriásica (APso) 4,40%; lupus eritematoso sistémico (LES) 3,37% y artritis idiopática juvenil (AIJ) 1,17 por ciento. Un análisis de 1.514 casos de la muestra total reportó que la tasa de incidencia para cualquier evento adverso es de 178/1.000 pacientes-año en TxB vs. 109/1.000 pacientes-año en controles con un riesgo relativo (RR) de 1,6 (IC del 95%, 1,4-1,9); para eventos adversos graves un RR de 15,4 (IC del 95%, 3,7-63,0 p < 0,0001). La supervivencia global de TxB es del 80% a 12 meses, el 61% a 24 meses, el 52% a 36 meses y el 45% a 48 meses. La tasa de mortalidad estandarizada (TME) es de 0,23 (IC del 95%, 0,0-49,0) para TxB vs. 0,00 (IC del 95%, 0,0-0,2) para controles. Se concluye que la TxB se asocia a un mayor riesgo de presentar eventos adversos, especialmente infecciosos, en comparación con pacientes sin TxB. La mortalidad de los pacientes expuestos a TxB no es mayor que la esperada para la población general ajustada a edad y sexo.

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* Corresponding author.
E-mail addresses: mavis.goycochea@gmail.com, mavis@reumatologia.org.mx (M.V. Goycochea-Robles).

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Introduction

Rheumatic diseases affect more than 10% of the general population.[1] Mexico has identified a high prevalence of major rheumatic diseases: in particular, the prevalence of rheumatoid arthritis is estimated 1.60% (95% CI 1.4–1.7),[2] in our environment, and is one of the main demands of attention in primary care and a cause of the high cost of health[3] services.

The treatment of these diseases is complex, since it requires multidisciplinary and early management which should include nonpharmacologic measures, such as physical, occupational and psychological and drug treatments with different mechanisms of action, such as the chronic use of analgesics, nonsteroidal antiinflammatory drugs (NSAIDs) and even glucocorticoids. The cornerstone of management is the early introduction of disease modifying drugs (DMARDs) such as methotrexate, antimalarials, sulfasalazine and leflunomide.[4,5] During the last decade the options of DMARDs have increased, with the development of promising new drugs, including biological agents that usually consist of monoclonal antibodies directed to specific molecules such as tumor necrosis factor (anti-TNF-α), interleukin receptor (IL-1 and IL-6), B cells and regulators of T cell costimulation[6] and many more in development.

Numerous clinical trials have demonstrated the efficacy and safety of biologic[7] therapy, but long and medium term follow-up of these cases has been limited.[8] Consequently, assessments in real scenarios are necessary to determine the efficacy and safety of this drug class in clinical practice and to this end different registries have been carried out,[9,10] mostly in developed countries, but the results have been highly variable, due to different methodologies and analysis, plus they should consider the demographic, socioeconomic and medical care of each society, especially those with emerging economies, where there are important differences to biological therapy, such as cost and access of these drugs. In addition, the epidemiological scenario is different from that reported in developed societies regarding an increased risk of infections. Therefore, the purpose of this report is to describe the adverse events reported in a cohort of Mexican patients with rheumatic diseases treated with biologic agents and identify the survival rate of the same and causes of discontinuation of therapy.

Methods

The platform for the registration of patients using biological therapy is that of the Spanish Society of Rheumatology (SER), used since 2000,[11] considered by PANLAR Biobadamérica for development of the project, whose main objective is to get local records relating to the use of biologics in Latin America and in which each country adopts the registry with appropriate modifications.

The Mexican College of Rheumatology (CMR) initiated a retrospective registry (RECOLBI) in 2007 of cases of patients with rheumatic diseases treated by specialists in rheumatology with biologic drugs, and since 2008 has used the BIOBADASER Biobadamex[12,13] platform, which also included a control group of patients with the diagnosis of rheumatoid arthritis (RA) treated with non-biological DMARDs. This was possible due to the different health care systems in the country, because not all systems covered biological therapy, such as some hospitals of the Ministry of Health as well as private care, where access depends on the direct purchase of treatment by the patient.

Patients with any kind of rheumatic disease that warranted the use of biologic therapy were considered candidates to enter the registry. Minimum follow up time in order to be added to the registry was one year from the date of onset of biological drug. The protocol was approved and registered (2009-785-103) in the Mexican Social Security Institute.

Certified rheumatologists in the country were invited to participate in the registry and include a minimum of 20 cases with no maximum. After remote (by telephone or via the Internet) or face to face training, each researcher was assigned a password; in this way, each specialist registered cases diagnosed and treated with biological agents online at their leisure (except for cases that were included in treatment protocols or were part of a clinical trials) who had at least one year of follow-up. For quality control we carried out an online review of 100% of the cases and then subjected them to monitoring. Each center was monitored locally, and a monitor visited the center to randomly check a sample of at least 25% of cases. If more than 25% of inconsistencies were found, the case was removed from the registry.

Baseline: the registry consists of an electronic platform in which baseline data such as demographic characteristics were entered: age, sex, education, healthcare system, clinical parameters of the disease: diagnosis, duration, activity in cases of RA (DAS28) and ankylosing spondylitis (BASDAI), comorbidity, prior treatment for rheumatic disease and concomitant therapy, as well as information related to the biological agent: type of drug (adalimumab, abatacept, etanercept, infliximab, rituximab), drugs available in Mexico during this phase of registration, also including the date of onset and discontinuation of treatment and the cause in case of discontinuation. Each patient attended a scheduled appointment with the attending rheumatologist and was followed with a frequency individualized according to the discretion of each physician, without following previously set intervals.

In this study, all adverse events considered harmful or undesirable after the administration of a drug, at doses commonly used to prevent, diagnose or treat a disease, or to modify any biological function were registered. Serious adverse event was defined as any unfavorable event, regardless of dose, with life-threatening characteristics, which required hospital admission or prolonged hospitalization, as well as producing persistent or significant disability; a fatal adverse event was every unfavorable event regardless of dose, that was fatal. We used the nomenclature of MedDRA (Medical Dictionary for Drug Regulatory Activities) to classify each of the adverse events.

During follow-up, evaluations of adverse events associated with the use of biologic therapy were recorded and, if they occurred, changes in biological treatment schemes were filed. Minimum follow-up of the patient in order to report adverse events or changes in the biologic was of one year. Because the temporary registration was both retrospective and prospective, if a patient already had a one-year period on the biological drug, the patient could be considered in the analysis, but if the time to include the patient still did not meet this interval, patient follow-up continued for at least 12 months.

Statistical analysis: This report includes a first descriptive analysis of 2047 patients at baseline through February 2011, considering their demographic information, clinical features and treatment. The second phase of analysis consisted of 1514 of the total 2047 cases, which correspond to cases monitored, including in this group those receiving biological therapy (n=1114) vs a control group of patients with RA treated with non-biological DMARDs (n=400), analyzing the results using the Student t test, ANOVA for continuous variables and χ^2 test for qualitative variables. This same subsample of 1514 cases was used to identify the risk of an adverse event between the biological vs. non-biological group treated with DMARDs alone; we calculated the incidence rate of adverse events per 100 000 patient-years (95%). Standardized rates were calculated adjusted for age and sex in general Mexican population. Finally, survival with the drug was identified through the Kaplan–Meier method, including those treated with anti-TNF, considering variable census