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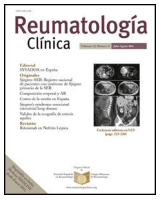

Brief Report

Survival of first line biological and targeted synthetic disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis in Chile

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ABSTRACT

Introduction: In Chile, patients with refractory rheumatoid arthritis (RA) are candidates for treatment with biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs). Due to the cost and diversity of drugs currently available to treat RA, there is a greater need to evaluate their survival in the real world and mainly to provide local and national data.
Objectives: To describe the survival and cause of discontinuation/change of first line b/tsDMARDs in patients with active refractory RA at the rheumatology clinic of the Regional Hospital of Copiapó.
Materials and methods: Patients with refractory RA on first-line treatment with b/tsDMARDs were included. Data were obtained from the RA registry of patients from January 01, 2018, until July 31, 2023, and by reviewing medical records. Demographic and clinical characteristics of the patients, survival of b/tsDMARDs, and cause of discontinuation/change of therapy are described. Kaplan–Meier plots and log-rank tests were performed. Cox model was used to identify factors that affected treatment discontinuation.
Results: One hundred thirty patients met the selection criteria. Survival of the different treatments was calculated, excluding rituximab and tocilizumab due to n <10. There were no significant differences between the survival of the groups (anti-TNF, abatacept, tofacitinib), with $p > 0.05$. The mean survival time for b/tsDMARDs was 194 weeks. In this cohort, 34.62% ($n = 45$) of the patients had treatment discontinuation/change, with lack of efficacy representing 80%.
Conclusion: In this cohort of patients with RA, there were no statistically significant differences in survival after first-line treatment with b/tsDMARDs. The choice of initial therapy will depend on multiple clinical, demographic, economic and regulatory factors.

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Supervivencia de terapias antirreumáticas de primera línea con fármacos biológicos y sintéticos dirigidos en pacientes con artritis reumatoide en Chile

Palabras clave:
Artritis reumatoide
Supervivencia
Fármacos antirreumáticos biológicos y terapia dirigida
Terapia primera línea

RESUMEN

Introducción En Chile los pacientes con artritis reumatoide (AR) refractaria son candidatos a tratamiento con fármacos antirreumáticos modificadores de la enfermedad biológicos y sintéticos dirigidos (b/tsDMARDs). Tanto por el costo como por la diversidad de los medicamentos disponibles actualmente para tratar la AR, existe una mayor necesidad de evaluar su supervivencia en el mundo real y particularmente aportar datos locales y nacionales.
Objetivos: Describir la supervivencia y la causa de suspensión/cambio de terapia de primera línea con b/tsDMARDs en los pacientes con AR refractaria activa, atendidos en la consulta de reumatología del Hospital Regional de Copiapó.

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Materiales y métodos: Se incluyeron pacientes con AR refractaria, en tratamiento de primera línea con b/tsDMARDs. Los datos se obtuvieron del registro de pacientes con AR desde el 1 de enero 2018 hasta el 31 de julio de 2023, y mediante revisión de historias clínicas. Se describen las características demográficas/clínicas de los pacientes; sobrevida de b/tsDMARDs y causa de suspensión/cambio de terapia. Se realizaron gráficos de Kaplan-Meier y test de *log-rank*. El modelo de Cox fue usado para identificar los factores que afectaron en la discontinuidad del tratamiento.
Resultados: Ciento treinta pacientes cumplieron los criterios de inclusión. Se calculó la supervivencia de los diferentes tratamientos, excluyendo rituximab y tocilizumab por n < 10. No hubo diferencias significativas entre la supervivencia de los grupos (anti-TNF, abatacept, tofacitinib), siendo p > 0,05. El tiempo medio de supervivencia para b/tsDMARDs fue de 194 semanas. El 34,62% (n = 45) de los pacientes presentó suspensión/cambio de tratamiento, representando la falta de respuesta el 80%.
Conclusión: En esta cohorte de pacientes con AR no hubo diferencias estadísticamente significativas en la supervivencia de tratamiento de primera línea con b/tsDMARDs. La elección de la terapia inicial dependerá de múltiples factores clínicos, demográficos, económicos y regulatorios.
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Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune and systemic inflammatory disease of unknown etiology; primarily affecting the joints and frequently evolving towards joint destruction and deformity.[1] Between 10 and 20% do not respond to therapy with traditional disease-modifying anti-inflammatory drugs (DMARDs).[2] In this group of patients, RA causes progressive joint damage and limitation in functional capacity, deteriorating their quality of life. Therefore, these patients constitute the candidate group for treatment with biological agents or Janus kinase inhibitors (JAKi).[2]

The use of biological therapies has represented a major change in the treatment of chronic rheumatic diseases, particularly RA. Regulating the inflammation with these drugs has allowed more patients to achieve remission or low disease activity.[3]

Biological DMARDs (bDMARDs) that can be used in these patients include TNF-α inhibitors (TNFi) such as adalimumab, etanercept, and golimumab; which prevent the TNF-alpha-mediated cellular response and modulate the biological response controlled by additional down-regulating molecules (e.g., cytokines, adhesion molecules, or proteinases) induced or regulated by TNF-α. Anti-IL-6 receptor antibodies such as tocilizumab; abatacept, a fusion protein that exerts its effect by inhibiting the co-stimulation mechanism, resulting in inhibition of T cell activity; and rituximab, a monoclonal antibody that binds to the CD20 antigen, which is predominantly expressed in mature B cells, inducing selective death by apoptosis of B cells.[2,4,5]

JAKi are small synthetic molecules, which selective inhibits the Janus kinase (JAK) family. Tofacitinib preferentially inhibits JAK1 and JAK3, which reduces interleukin and interferon signaling, thus modulating the inflammatory and immune response.[2,6] Since 2015, due to the promulgation of Law 20,850 (Ricarte Soto Law, LRS) in Chile, which provides free coverage for high-cost treatments for patients with different pathologies, patients with active refractory RA are candidates for treatment with biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs). JAKi inhibitor tofacitinib is available since 2019.[2]

These drugs play an essential role in the treatment of RA. However, it must be taken into account that they have different mechanisms of action, there may be differences in adverse effects, and they are also expensive, although the biosimilars currently available have improved the cost/benefit ratio. Since there are multiple drugs available to treat RA, it is very important to assess their survival in the real world. Multiple studies and national registries have reported survival rates for b/tsDMARDs in patients with RA.[7–13] However, treatment survival rates may vary by multiple factors, including demographic factors, clinical characteristics of the patients, access to treatment regulations, distance from care center, and frequency of follow-up, among others.[9] Therefore, it is interesting to provide local and national data that reflects the reality of our patients. The following objective is proposed:

To describe the survival and cause of discontinuation/change of first line b/ts DMARDs in patients with active refractory RA at the rheumatology clinic of the Regional Hospital of Copiapó (RHC), Atacama, Chile.

Materials and methods

Patients selection

Patients with active refractory RA ≥18 years on first-line treatment with b/ts DMARDs attended at the rheumatology clinic of the RHC were included. The diagnosis of RA was according to ACR/EULAR 2010 classification criteria[14] and active refractory RA was defined according to LRS criteria.[2] Patients with active refractory RA should meet the following criteria: 1. Active RA is defined as DAS28VHS >5.1 on two assessments, which must be performed at least 30 days apart and a maximum of 120 days apart. 2. Refractoriness to standard treatment: presence of active arthritis, despite appropriate use of at least three DMARDs, including at least two of the following: methotrexate, leflunomide, and sulfasalazine, administered at maximum doses, for a period of 6 months, unless there has been documented toxicity or intolerance to these doses.

Data was obtained from the registry of patients with RA admitted to the LRS since January 01, 2018 until July 31, 2023 and by reviewing electronic medical records. Demographic and clinical characteristics of the patients, current treatment, start date and date of discontinuation of therapy, and cause of change/discontinuation of therapy were recorded.

Data analysis

The average, percentage, and standard deviation were calculated for categorical variables. The Kaplan–Meier estimator[15] was used for the curve graph, and the same estimator was used to calculate the mean and median survival. Patients still receiving treatment at the time of study closure were recorded as right censoring. The log-rank test was used to compare curves. A semi-parametric estimate (Cox model)[16] was also performed. *p*-Values ≤0.05 indicate statistical significance. R software v. 4.3.1[17] was used for statistical analysis.

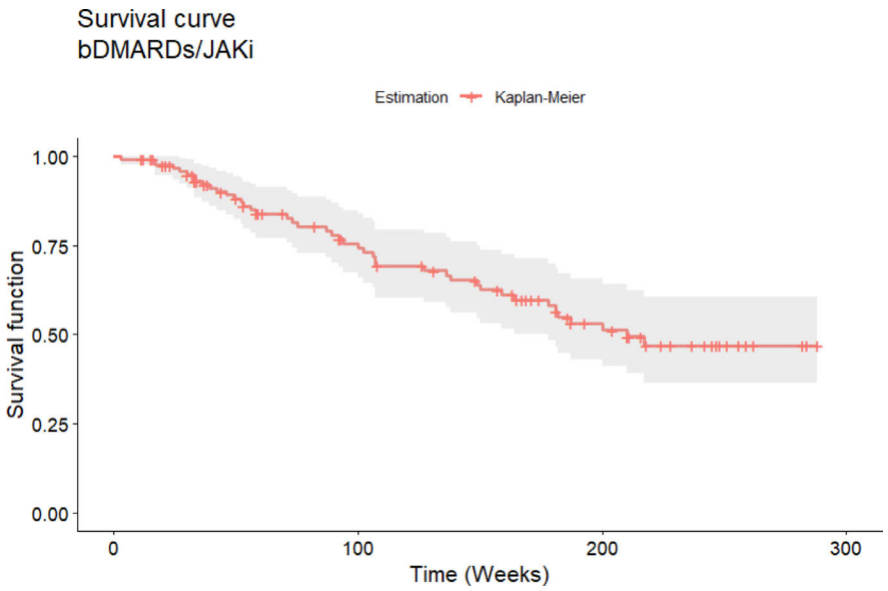

Fig. 1. bDMARDs/JAKi survival curve.

Table 1
Demographic and clinical characteristics, $n = 130$.

Age in years, mean SD	61.58 ± 10.58
Female, *n* (%)	117 (90%)
FR positive, *n* (%)	111 (85.38%)
Anti-CCP positive, *n* (%)	108 (83.07%)
FR and anti-CCP positive, *n* (%)	101 (77.69%)
Smoking, *n* (%)	30 (23.07%)
PPD positive, *n* (%)	22 (16.92%)
Duration of disease in years, mean SD	14.61 ± 7.21
Initial DAS28VHS, mean SD	6.3 ± 0.52
Last control DAS28VHS, mean SD	4.04 ± 0.99
Initial HAQ, mean SD	1.56 ± 0.50
Last control HAQ, mean SD	0.93 ± 0.43
Corticosteroid use, *n* (%)	81 (62.3%)
Prednisone or equivalent dose, mg/day, mean SD	4.13 ± 1.65
Anti-TNF therapy, *n* (%)	89 (68.46%)
Etanercept = 42	
Adalimumab = 36	
Golimumab = 11	
Abatacept, *n* (%)	21 (16.15%)
Tofacitinib, *n* (%)	12 (9.23%)
Rituximab, *n* (%)	4 (3.08%)
Tocilizumab, *n* (%)	4 (3.08%)

Results

Demographic and clinical characteristics

One hundred thirty patients were included. The demographic and clinical characteristics are described in Table 1. The mean age was 61.58 years and 90% were female patients; in this cohort most patients were seropositive RA, with a mean duration of disease 14.61 years (long lasting RA). 62.3% of patients were on corticosteroid treatment. Anti-TNF therapy was the most frequent, representing 68.46%. When comparing the values obtained from DAS28VHS and HAQ between the first and last control, a reduction of 35.87% and 40.38% was observed, respectively. This would reflect the effectiveness of the treatments used in the patients. See Table 1.

Nonparametric estimation

Survival of bDMARDs /JAKi was calculated using the Kaplan–Meier curve. See Fig. 1.

According to the Kaplan–Meier estimator, the survival rate for b/ts DMARDs is 87.1% up to week 52 (1 year), 73.1% by week 104 (2 years), 62.6% by week 156 (3 years), 47% by week 217, and remains at that level until the end of data collection. The mean survival time for b/tsDMARD therapies is 194 weeks, and the median time is 210 weeks.

Comparison of b/tsDMARD curves

In this calculation, treatments with rituximab and tocilizumab were excluded because *n* was less than 10, going from 130 patients to 122 to create the curves. As observed in Fig. 2, when comparing by groups (anti-TNF therapy, abatacept, tofacitinib), there is no significant difference between the different curves, and this is reinforced when performing the log-rank test, which gives a *p*-value of 0.2. The average survival time for etanercept was 186 weeks ±86, adalimumab 179 weeks ±108, golimumab 103 weeks ±61, abatacept 184 weeks ±53, and tofacitinib 179 weeks ±32. In addition, therapies were compared individually, with the difference between the curves for abatacept and golimumab being significant using the log-rank test, reporting a *p*-value of 0.03.

A semi-parametric estimation (Cox model) was performed, starting with the full model where all b/tsDMARD were considered, proceeding to remove those that are not significant from the model, obtaining that only the therapies golimumab and abatacept were significant at 5%, with golimumab having a *p*-value of 0.0371 (using abatacept as a base), see Table 2. Regarding the validation of the model, it complies with the assumption of the proportional risk with a *p*-value of 0.2.

A significant difference was observed between golimumab and abatacept when estimating survival rates for the therapies using Kaplan–Meier and Cox. Patients treated with golimumab had a lower survival rate, indicating that in this cohort this treatment had a lower efficacy and/or a higher rate of adverse effects than abatacept. This result would agree with a meta-analysis study,[11] which found a lower presence of adverse events when comparing abatacept vs TNFi.

Cause for discontinuation/change of treatment

Treatment discontinuation/change occurred in 34.62% ($n = 45$) of patients; with lack of efficacy representing 80% ($n = 36$) and

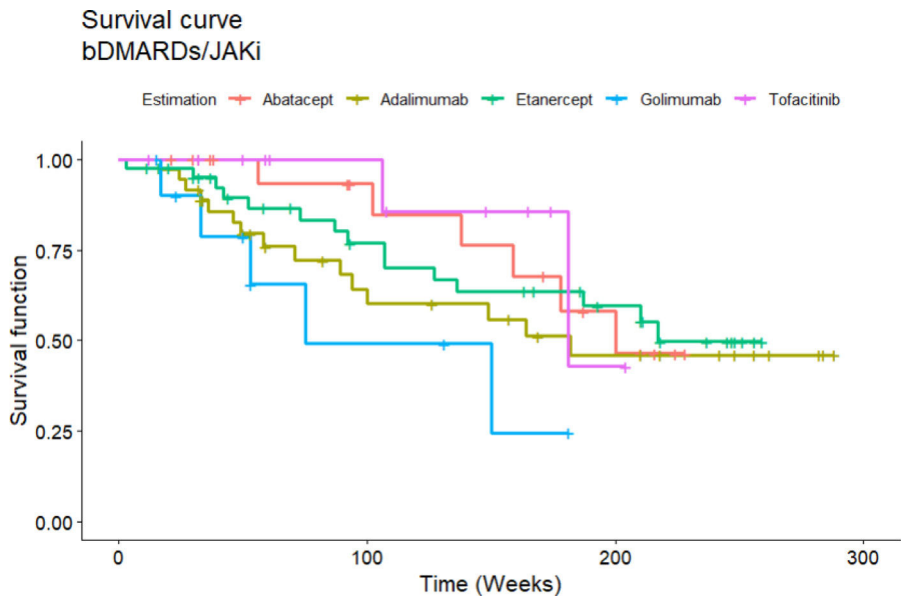

Fig. 2. Comparison of b/tsDMARD curves.

Table 2
Results from the Cox model of golimumab semi-parametric estimation (Cox model).

Therapy	Coefficient	Exp (coef.)	Standard error	*Z*-statistics	*p*-Value
Golimumab	1.3519	3.8648	0.6484	2.085	0.0371

Table 3
Treatment discontinuation/change.

	No discontinuation	Discontinuation cause			
		Lack of efficacy	Neoplasia	ADR	ILD
Adalimumab	21	11	1	2	1
Etanercept	27	15	0	0	0
Golimumab	6	1	1	2	1
Abatacept	15	6	0	0	0
Tofacitinib	11	0	0	1	0
Rituximab	3	1	0	0	0
Tocilizumab	2	2	0	0	0
Total	85	36	2	5	2

Note: "No discontinuation" refers to those patients who continued with the active treatment at the end of the observation period.

27.70% of the total patients, adverse drug reaction (ADR) 11.11% ($n = 5$), and other causes such as neoplasia, interstitial lung disease (ILD) and death 13.33% ($n = 6$). At the end of the study, 65.38% of the patients continued their first-line treatment ($n = 85$). See Table 3.

Discussion

The most commonly used therapy as a group was anti-TNF, representing 68.46% of patients. When analyzing the survival of first-line treatment of b/tsDMARD therapies in patients with RA, in this cohort the mean survival time was 194 weeks. It should be noted that given the *n* less than 10 for tocilizumab and rituximab (both $n = 4$) in this study, these data should not be generalized to these treatments. Favalli et al.,[8] reported for anti-TNF therapy in RA a median survival of 232 weeks (120 for adalimumab, 192 for infliximab, and 232 for etanercept). Similarly, Brodszky et al., reported for first-line treatment, the median survival time for infliximab, adalimumab, and etanercept of 74, 73, and 78 weeks respectively.[9] In the Biobadaguay registry the mean survival for bDMARDs in patients with RA was 289 weeks.[10] The median drug survival (95% CI) for all tofacitinib-treated patients was reported in 255 (245, 265) weeks and the estimated 2 and 5 year drug survival rates were 75.5% and 49.4%, respectively.[18] These previous data are comparable for this cohort, where it is observed that our results on median survival are within an acceptable range of weeks.

There were no statistically significant differences in survival between the different therapy groups. However, there were significant differences in survival rates between golimumab and abatacept. Other studies had reported higher survival rates for non-anti-TNF therapies vs anti-TNF therapies.[9,11,12,19,20] In this study, the difference in the survival rate of golimumab compared to abatacept can be explained by the low number of patients on treatment with golimumab ($n = 11$); besides five patients had treatment discontinuation/change (see Table 3), which was an unusual percentage of withdrawal (45%) compare to the other therapies in this study and with reported withdrawals in clinical trials of golimumab.[5] *Note*: Due to the small sample size for golimumab, caution is advised when considering these results for potential conclusions, as they may be biased.

Treatment discontinuation/change to first-line treatment was reported in 34.62% of patients, with lack of efficacy representing the highest percentage of changes (80%), comparable to that reported in other studies.[7–12,19,20]

In conclusion, there were no statistically significant differences in the survival rate for first-line b/tsDMARD treatment in this cohort of patients with RA. The choice of initial therapy will depend on multiple clinical, demographic, economic, and regulatory factors.

Conflict of interests

The authors have no conflict of interest to declare.

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