research orientation; critical review of the literature; critical review of the manuscript.

Leonardo Peruilh-Bagolini: Approval of the final version of the manuscript; conception and planning of the study; elaboration and writing of the manuscript; obtaining, analyzing, and interpreting the data; effective participation in research orientation; critical review of the manuscript.

Fernando Valenzuela: Approval of the final version of the manuscript; conception and planning of the study; obtaining, analyzing, and interpreting the data; effective participation in research orientation; critical review of the manuscript.

Conflicts of interest

None declared.

References

1. Abbasi NR, Shaw HM, Rigel DS, Friedman RJ, McCarthy W, Osman I, et al. Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. JAMA. 2004;292:2771–6.
2. Bono A, Tolomio E, Trincone S, Bartoli C, Tomatis S, Carbone A, et al. Micro-melanoma detection: a clinical study on 206 consecutive cases of pigmented skin lesions with a diameter < or = 3 mm. Br J Dermatol. 2006;155:570–3.
3. Seidenari S, Ferrari C, Borsari S, Fabiano A, Bassoli S, Giusti F, et al. Dermoscopy of small melanomas: just miniaturized dermoscopy? Br J Dermatol. 2014;171:100613.
4. Pellizzari G, Magee J, Weedon D, Rosendahl C. A tiny invasive melanoma: a case report with dermatoscopy and dermatopathology. Dermatol Pract Concept. 2013;3:4951.
5. Drugge ED, Volpicelli ER, Sarac RM, Strang SR, Elston DM, Drugge RJ. Micromelanomas identified with time-lapse total body photography and dermoscopy. J Am Acad Dermatol. 2018;78:182–3.
6. Goldsmith SM, Solomon AR. A series of melanomas smaller than 4 mm and implications for the ABCDE rule. J Eur Acad Dermatol Venereol. 2007;21:929–34.
7. Megaris A, Lallas A, Bagolini LP, Papageorgiu C, Spyridis I, Apalla Z. Dermatoscopic features of melanomas with a diameter up to 5 mm (micromelanomas): a retrospective study. J Am Acad Dermatol. 2020;83:1160–1.

Pablo Vargas-Mora *, Rubén González-Cuevas, Leonardo Peruilh-Bagolini, Fernando Valenzuela

Department of Dermatology, Faculty of Medicine, Universidad de Chile, Santiago, Chile

* Corresponding author.
E-mail: pablovargas.med@gmail.com (P. Vargas-Mora).

Received 22 August 2020; accepted 5 October 2020
available online 20 November 2021

https://doi.org/10.1016/j.abd.2020.10.014

Therapeutic response and survival time of immunobiologicals in patients with moderate to severe psoriasis☆

Dear Editor,

Psoriasis is an inflammatory, chronic and recurrent disease with evident genetic influence. The intensity, extension and different manifestations associated with the disease guide therapeutic decisions. Advances in the knowledge of the disease immunopathology over the last decades have culminated in the development of new medications, called immunobiologicals, which act in a specific and precise way at different levels of the inflammatory cascade of psoriasis.[1] With the introduction of anti-tumor necrosis factor-alpha (anti-TNF-α) drugs: etanercept (ETA), infliximab (INF), adalimumab (ADA), and certolizumab pegol (CP), followed by inhibitors of interleukin-12/23, ustekinumab (UST); inhibitors of interleukin 17: secukinumab (SEC) and Ixekizumab (IXE), and more recently inhibitors of interleukin 23 alone: Guselkumab (GUS) and Risankizumab (RISA), it has become possible to effectively treat severe and refractory forms of the disease, associated with a satisfactory safety profile. On the other hand, uncertainty regarding the choice of the most appropriate drug, the long-term sustained response, and the possibility of interrupting therapy has an impact on the therapeutic decision.

Drug survival is defined as the time from the beginning to the discontinuation of a certain treatment. The time interval from the start of the treatment to its discontinuation, as well as the reasons for this outcome, whether due to loss of efficacy, complications, or treatment abandonment, may vary in different populations with psoriasis.[2,3] To date, there are no data associating the therapeutic response to the survival time of immunobiologicals in patients with psoriasis in Brazil.

Aiming to determine the time of drug survival, a total of 229 treatments with immunobiological drugs were evaluated in 110 patients with moderate to severe psoriasis at Hospital das Clínicas, Universidade de São Paulo, in the state of São Paulo, Brazil, for a period of two years and analysed regarding the response to immunobiologicals, number of previous treatments and reason for discontinuation. The analysis of medical records also allowed the collection of data in relation to previous treatments since the introduction of immunobiologicals as a therapeutic option. Drug survival was defined as the time from the start of the treatment with the immunobiological, that is, the first dose until the occurrence of the event of interest (temporary/definitive discontinuation of treatment). Kaplan-Meier curves were used to estimate each of the drug survival prob-

☆ Study conducted at the Hospital das Clínicas da Universidade de São Paulo, São Paulo, SP, Brazil.

Table 1 Reasons for temporary interruption of treatments.

	Reasons	n (%)
n = 229	Failure of supply in SUS	76 (33.2)
Treatments	Others[a]	9 (3.9)
	Pregnancy	3 (1.3)
	Lost to follow-up	3 (1.3)
	Surgery	2 (0.9)
	Repeated UAIs	2 (0.9)
Total		95 (41.5)

SUS, *Sistema Único de Saúde*; UAIs, Upper Airway Infections.
[a] Others: Nonspecific symptoms such as headache, myalgia, arthralgia, nausea.

Table 2 Reasons for definitive interruption of treatments.

	Reasons	n (%)
n = 229	Secondary failure	61 (26,6)
Treatments	Others	19 (8,3)
	Primary failure	12 (5,2)
	Failure of supply in SUS	12 (5,2)
	Tuberculosis	8 (3,5)
	Pregnancy	4 (1,7)
	Protocol	2 (0,9)
	Stomach cancer	1 (0,4)
	Hernia surgery	1 (0,4)
	Hepatotoxicity	1 (0,4)
	UAI	1 (0.4)
	Infusion reaction	1 (0.4)
Total		123 (53.7)

Others, Headache, nausea, myalgia, and arthralgia; SUS, Unified Health System; Protocol, Patients who used infliximab only in the induction phase to control erythrodermic psoriasis; UAI, Upper Airway Infection.

abilities and the difference between the drug survival curves was verified using the logrank test.

The comparative analysis between the five immunobiologicals showed that SEC was the drug with the longest time of survival, including 22 treatments (9.6%), followed by UST with 64 treatments (28%), ADA with 52 treatments (22.7%), ETA with 56 treatments (24.4%), and INF with 35 treatments (15.3%) (Fig. 1). Second-line cases showed lower drug survival compared to first-line cases, whereas third-line cases had lower survival compared to second-line cases, and so forth. Isolated analyses regarding the first and second-line drugs depicted Kaplan-Meier curves showing that UST had a higher probability of drug survival, with fewer failures. INF showed a lower probability of drug survival in two years, with more failures. These differences were shown to be statistically significant (Fig. 2).

Among the factors that led to treatment interruption, present in 95 of a total of 229 treatments (41.5%), the most frequent cause of temporary interruption was the lack of medication supply, observed in 76 of the analyzed cases (33.2%) (Table 1), whereas among the causes of definitive interruption, observed in 123 of a total of 229 treatments (49.6%), the main cause was a secondary treatment failure, observed in 26.6% of the analyzed treatments (Table 2). Overall, the primary failure was considered when the patient did not show a PASI50 response after 24 weeks of treatment and occurred in 5.2% of cases. When analyzing the results, one should consider the small number of cases treated with SEC, a drug that was only approved in Brazil in 2016. Similarly, data from more recently approved immunobiologicals such as CP, IXE, GUS, and RISA are not included in the results of this study.

According to the literature, one of the main causes for the discontinuation of an immunobiological is the loss of efficacy, also called secondary failure.[4,5] Our results demonstrate in an unprecedented way that the medication supply failure was the main reason for the temporary interruption of treatments. It is noteworthy that, when resuming the immunobiological treatment after a prolonged interruption, the chance of a lower response should always be considered.[6,7] These facts reinforce the importance and need for continuous and regular provision of these medications by the providers.

The occurrence of tuberculosis leading to treatment discontinuation was exclusive to anti-TNFs, as well as the few cases of infusion reaction, UAIs, hepatotoxicity, and cancer. The lack of medication in the Brazilian Unified Health System (SUS, *Sistema Único de Saúde*), leading to the definitive interruption of the therapy, was more frequent with UST and SEC. Regarding the main cause of discontinuation, secondary failure occurred with all immunobiologicals, with a variation only in the time of its occurrence.

The results shown here provide a regional analysis of the time of survival of immunobiological drugs and the main reasons for treatment discontinuation in a public institution, which can help in the planning and monitoring of treatments with immunobiologicals, both by the prescribing physicians and the health managers.

Financial support

None declared.

Authors' contributions

Cynthia Cristina Ferreira Mota: Terminology, conceptualization, methodology, investigation, resources, data curation, writing-original draft, visualization, project administration.

Ricardo Romiti: Methodology, investigation, writing review and editing, supervision.

Marcelo Arnone: Investigation.

Andre Luís da Silva Hirayama: Investigation.

Maria Denise Fonseca Takahashi: Investigation.

Conflicts of interest

None declared.

References

1. Conrad C, Gillet M. Psoriasis: from pathogenesis to targeted therapies. Clin Rev Allergy Immunol. 2018;54:102–13.
2. Carrascosa JM, Notario J. Drug survival in biologic therapy: do we know what it means? Can we calculate it? Actas Dermosifiliogr. 2014;105:729–33.

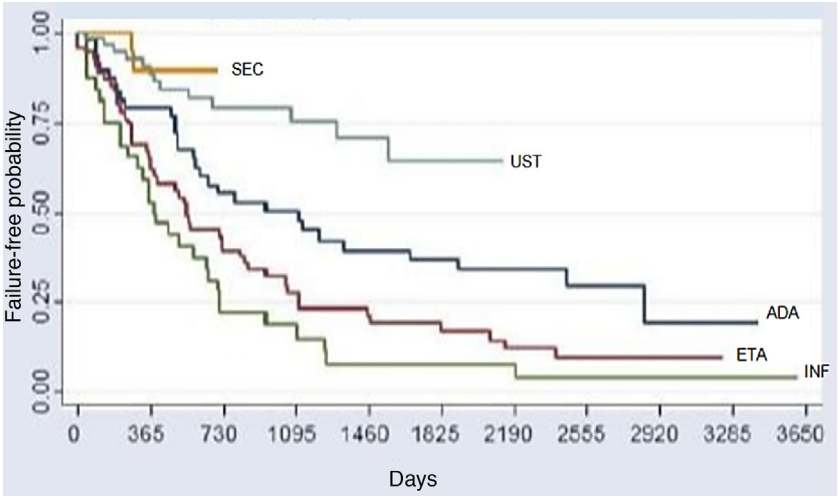

Figure 1 Kaplan-Meier curve for all treatments ($p < 0.001$). This chart reflects a better performance of secukinumab, followed by UST (second place), ADA (third place), ETA (fourth place), and INF (fifth place) over the period of 2 years (730 days). Through the analysis of the medical records, it was possible to assess the survival of some immunobiologicals for a period of up to 10 years (3,650 days).

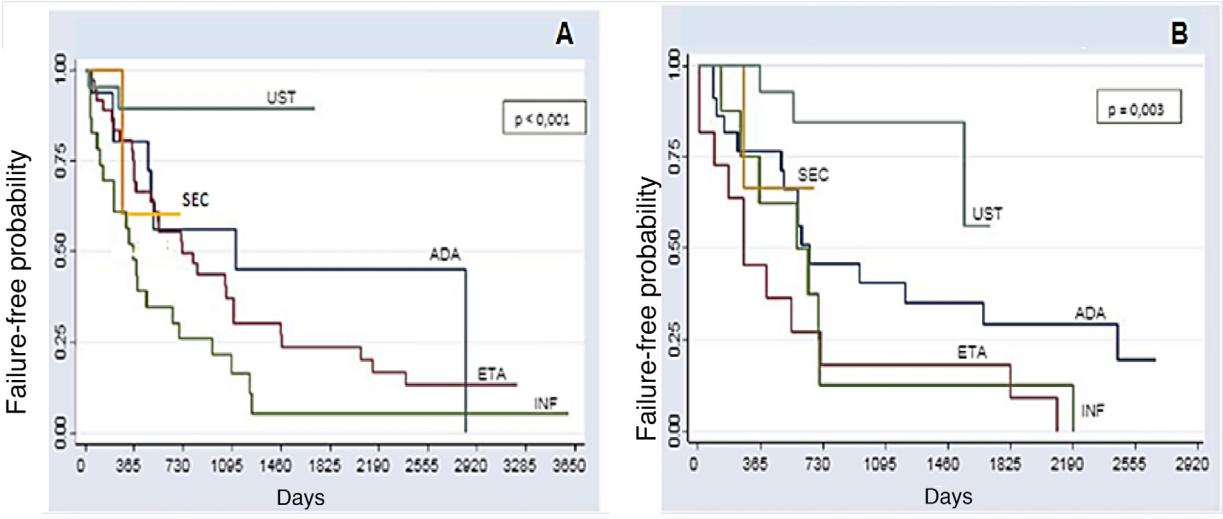

Figure 2 Kaplan-Meier curves for the treatments. (A), first-line (naïve) ($p < 0.001$); (B), Second-line ($p = 0.003$) in two years (730 days). In the first- and second-line groups, UST shows a higher probability of drug survival in two years; 89.2% and 83.3% respectively. INF shows a lower probability of drug survival in two years in the first and second-line groups (26.1% and 12.5%, respectively), with more failures. Through the analysis of the medical records, it was possible to assess the survival of some immunobiologicals for a period of up to 10 years (3,650 days).

3. Esposito M, Gisondi P, Cassano N, Ferrucci G, Del Giglio M, Loconsole F, et al. Survival rate of antitumour necrosis factor-α treatments for psoriasis in routine dermatological practice: a multicentre observational study. Br J Dermatol. 2013;169:666–72.
4. Menter A, Papp KA, Gooderham M, Pariser DM, Augustin M, Kerdel FA, et al. Drug Survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JEADV. 2016;30(7):1148–58.
5. Vilarrasa E, Notario J, Bordas X, López-Ferrer A, Gich IJ, Puig L. ORBIT (Outcome and Retention Rate of Biologic Treatments for Psoriasis): a retrospective observational study on biologic drug survival in daily practice. J Am Acad Dermatol. 2016;74:1066–72.
6. Ben-Horin S. Loss of response to anti-Tumor Necrosis Factors: What is the next step? Dig Dis. 2014;32:384–8.
7. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol. 2016;7:e135.

Cynthia Cristina Ferreira Mota [a,b,*], Ricardo Romiti [c], Marcelo Arnone [c], Andre Luís da Silva Hirayama [c], Maria Denise Fonseca Takahashi [c]

[a] *Specialty Outpatient Clinic, Prefeitura Municipal de Santos, Santos, SP, Brazil*
[b] *Psoriasis Outpatient Clinic, Prefeitura Municipal de Santos, Santos, SP, Brazil*
[c] *Psoriasis Outpatient Clinic, Hospital das Clínicas da Universidade de São Paulo, São Paulo, SP, Brazil*

[*] Corresponding author.
E-mail: cynthiamota@santos.sp.gov.br (C.C. Mota).

Received 3 December 2020; accepted 4 March 2021
available online 20 November 2021

https://doi.org/10.1016/j.abd.2021.03.008

Trends in melanoma incidence at Hospital Italiano de Buenos Aires, 2007–2016[☆]

Dear Editor,

There are three types of melanomas: uveal, mucosal, and cutaneous. Cutaneous melanoma is the most common subtype, and it causes most skin cancer deaths.[1] Despite the fact that the risk factors for melanoma are known today and there are social prevention and advertising campaigns about skincare, disease rates have increased worldwide in recent years.[2] The demographic distribution of melanoma incidence is directly related to environmental and genetic factors such as geographic sun intensity, and skin phototypes of the population. Immunosuppression and numerous episodes of sunburn increase the risk even more.[3]

The Hospital Italiano de Buenos Aires is a private health care institution where approximately 300,000 people from Buenos Aires City (BA) are treated annually. Half of them are members of the prepaid Plan de Salud del Hospital Italiano de Buenos Aires (Medical Care Program – HMCP).[4] As little is known about melanoma incidence either in the BA or the Argentinean populations, we sought to explore that incidence in our HMCP population.

The Hospital Italiano de Buenos Aires Clinical Research and Bioethics Committee approved this study.

Rates were reported with the corresponding 95% Confidence Intervals (CIs). The differences were considered significant when the p-value was less than 0.05; STATA software (Stata Corp LLC, TX; version 14.2) was used for calculations.

A retrospective cohort study was carried out, including a population with reports of invasive cutaneous melanoma in our hospital between January 1, 2007, through December 31, 2016. We excluded those with just in situ melanoma or a primary report of metastasis of melanoma. The study population consisted of 163,100 members of the HMCP.

We found 253 cutaneous malignant melanoma (CMM) cases, witch 124 were females (49.0%). The median age at diagnosis was 69 years (IQR 58–78), and the average age at diagnosis was 66.3 years (SD=15.3). This result is in line with the higher incidence of CMM, as well as with other types of cancer, in older people. The average age of diagnosis for CMM worldwide is 57, while our data show a mean age of 66.[5]

The HCMP crude CMM incidence density rate (IDR) obtained was 19.5 per 100,000 person-years (95% CI 16.3–21.0). The adjusted IDR for the BA population was 13.4 per 100,000 person-years (95% CI 11.7–15.2). According to 2010 national demographic census data, BA has a population of 2,890,151 inhabitants, of which 30% are <25 years and 21.7% are >60 years. The distribution over age and gender strata are similar to the HMCP population (Fig. 1 a and b). The adjusted IDR for CMM for the population in Argentina is 10.2 per 100,000 person-years (95% CI 8.7–11.7), almost half of the crude HCMP IDR. This adjustment-based discrepancy can be attributed to the difference in the age distribution within the population under study, in which 32% of the members are over the age of 60 compared to the population of Argentina, which only has 10.2% belonging to the same age group.

Prevalence was estimated considering the number of live cases up to July 1, 2016, divided by the number of active HCMP members at that time. The prevalent cases were 193 out of 146,524 HCMP members with a prevalence rate of 13.2 per 100,000 people (95% CI 11.4–15.2).

When we analyze rates by gender, the literature says that in young people the incidence of CMM is higher in women. It is inverted in older people, with the higher incidence being in men.[6] In our population, we found a similar situation, HCMP gender-specific crude IDRs were 23.6 per 100,000 person-years (95% CI 18.7–26.8) for males and 15.9 per 100,000 person-years (95% CI 13.1–18.8) for females. The adjusted IDR for the BA population was 16.3 per 100,000 person-years (95% CI 12.4–20.2) and 12.3 per 100,000 person-years (95% CI 9.9–14.6), respectively (Table 1).

The incidence rate ratio (IRR) of the crude IDR for males compared to females was 1.5 (95% CI 1.2–1.9; p = 0.0017). This data suggests a higher probability of developing this type of tumor in men. This is probably due to fewer prevention strategies since, in our country, men were the ones primarily exposed to the sun for work reasons in past decades. In the meantime, the population of women has started increasing in this regard due to tanning beds and intermittent sun exposure for recreational or beauty purposes.[2,7]

On a worldwide level, we find a wide range of rates for CMM. The annual incidence ranges from 0.3 and 0.2 per 100,000 person-years in Asia and India, respectively, up to 55

[☆] Study conducted at the Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.