Revista Colombiana de
REUMATOLOGÍA
www.elsevier.es/rcreuma

Original Investigation

Biological therapy optimization in patients with psoriasis by reducing the dose or increasing the time interval, in a specialized centre in Colombia

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ARTICLE INFO

Article history:
Received 15 July 2022
Available online 12 May 2023

Keywords:
Psoriasis
Biological therapy
Dose tapering
Relapse
IL-16
IL-23

ABSTRACT

Introduction: Psoriasis is treated with biological therapy, which has led to low disease activity or even clinical clearance. The optimization (dose-tapping) process seeks to reduce biological therapy while maintaining the risk–benefit ratio.

Objectives: To determine relapse rate in psoriasis optimization strategy (dose tapering) patients.

Material and methods: Cohort study (October 2015 to February 2021) of patients with psoriasis in a specialized multicentre health institution in Colombia. Selection criteria included being at least 18 years old with biological therapy and having a sustained response (DLQI = 0–5; absolute PASI <3 or BSA <1) for at least 12 months. The optimization strategy was dose reduction or interval application increase. PASI >10 was defined as relapse. Rates were estimated by medication using Kaplan–Meier.

Results: Of the 467 patients with psoriasis in the cohort, 467 received biologic therapy. 12.2% ($n = 57$) of those who met the inclusion criteria were men, with a median age of 57 years (IQR: 44–66), disease evolution time of 15 years (IQR: 5–30), and time in optimization of 8 months (IQR: 1.54–13.2). Because of the increased application interval, the optimization strategy was 85.8%; 24.5% ($n = 14$) received ustekinumab, 35% ($n = 20$) received adalimumab, 15.8% ($n = 9$) received secukinumab, 14% ($n = 8$) received ixekizumab, 5.2% ($n = 3$) received etanercept, and 5.2% ($n = 3$) received guselkumab. A total of 14% (8 patients) relapsed, the relapse rate was 7.4 cases per 100 person-years (95% CI: 3.4–14).

Conclusions: Eighty-six percent of patients in the optimization strategy remain relapse-free after 8 months. The optimization strategy was effective, with a low relapse rate.

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https://doi.org/10.1016/j.rcreu.2023.02.012

Optimización de la terapia biológica en pacientes con psoriasis reduciendo la dosis o incrementando el intervalo de aplicación en un centro especializado en Colombia

Palabras clave:
Psoriasis
Reducción progresiva de la dosis
Terapia biológica
Recaída
IL-16
IL-23

RESUMEN

Introducción: La terapia biológica es efectiva en el tratamiento de la psoriasis, su optimización busca reducir la dosis sin afectar la relación riesgo-beneficio.
Objetivos: Determinar la tasa de recaída en pacientes con optimización.
Materiales y métodos: Cohorte (octubre 2015-febrero 2021) de pacientes con psoriasis en una institución de salud multicéntrica especializada en Colombia. Se incluyeron pacientes mayores de 18 años con terapia biológica y una respuesta sostenida (DLQI = 0-5; PASI absoluto <3 durante 12 meses). La estrategia de optimización fue la reducción de la dosis o el aumento del intervalo de aplicación. El PASI >10 se definió como recaída. Las tasas se estimaron por medicación utilizando Kaplan-Meier.
Resultados: De 467 pacientes con psoriasis y terapia biológica, se incluyó al 12,2% (n = 57). El 65% (n = 37) eran varones, con una edad media de 57 años (RIC: 44-66), un tiempo de evolución de la enfermedad de 15 años (RIC: 5-30) y un tiempo de optimización de 8 meses (IQR: 1,54-13,2). En el 85,8% de los casos se aumentó el intervalo de aplicación; el 24,5% (n = 14) recibió ustekinumab, el 35% (n = 20) adalimumab, el 15,8% (n = 9) secukinumab, el 14% (n = 8) ixekizumab, el 5,2% (n = 3) etanercept y el 5,2% (n = 3) guselkumab. El 14% (8 pacientes) recayó, en tanto que la incidencia fue de 7,4 recaídas por cada 100 personas/año (IC 95%: 3,4-14).
Conclusiones: El 86% de los pacientes en la estrategia de optimización permanece sin recaídas a los 8 meses. La estrategia fue efectiva y tuvo una baja tasa de recaída.

Introduction

Psoriasis affects between 0.5 and 2% of the world's population.[1] In some countries, biological therapies such as anti-tumor necrosis factor alpha (TNF), anti-interleukin 17 (IL-17), and anti-interleukin 23 (IL-23) are required for disease control in 25–40% of patients with moderate to severe psoriasis.[2,3] These treatments, in a high percentage of cases, achieve complete remission of lesions and symptoms.[4]

The optimal duration of the biological therapy is unclear beyond the clinical trial data; this justifies the evaluation of new therapeutic strategies in this regard.[5] Long-term immunomodulator therapy has safety implications, such as tuberculosis or candidiasis, among others.[6,7] Another consideration is the pharmacoeconomic impact of this type of therapy on the health-care system.[8]

Interventions for therapy optimization include lowering medication doses or increasing the time interval between applications.[9] The goal will be to achieve this lower dose while maintaining therapeutic goals in patients based on disease control.[10] Previous research has shown that 60% of maintenance is completed with this goal in mind.[11] This study aims to show the experience of a population in Colombia in which this treatment strategy has been implemented

Methods

Study objectives

The objectives were to: (1) determine the baseline characteristics of the dose-tapering strategy in psoriasis patients. (2) Investigate the dose-tapering frequency in biological therapy. (3) Determine the relapse rate in patients with psoriasis in the optimization strategy (dose tapering), defined as a Psoriasis Area Severity Index (PASI) >10 at the following period.

Study design and population

An open cohort study of outpatient adults with psoriasis was followed from October 2015 to February 2021 in a specialized multicenter health institution in Colombia with 11 outpatient healthcare facilities. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline was followed.[12] Patients eligible for the study were 18 years of age or older, had vulgar psoriasis, and were treated with biological therapy. Patients eligible for optimization therapy (dose tapering) were those with a sustained response (DLQI = 0–5; absolute PASI <3) for at least 12 months, and the intervention involved a change, a reduction in dose, or an increase in the interval between dose applications.

Data collection and analysis

The following period's sociodemographic (age, gender), clinical features (PASI, DLQI), treatment optimization, and relapse defined as a PASI >10 were extracted from the structured clinical record software HCM®. The implementation of a psoriasis integral healthcare model, which includes a standardized dermatologist consultation, ensures the evaluation of the clinical scores PASI and the Dermatology Life Quality Index (DLQI). The optimization (dose tapering) protocol was built by the dermatologist, rheumatologist, and knowledge management board with a systematic review of the literature and actual evidence. According to the severity of the disease, all patients were evaluated every 3–6 months.

Statistical analysis

Baseline characteristics and demographics were reported using descriptive statistics. The chi-square test was used to evaluate categorical variables if $n \geq 5$ and Fisher's exact test otherwise. If the assumption of normality was met or $n > 30$, the Student's *t*-test was used, otherwise the Wilcoxon rank sum test was used. Relapse rates were estimated by medication using Kaplan–Meier and the density incidence rate. The R statistical software version 4.2.1 was used.

Ethical considerations

The researchers adhered to the Declaration of Helsinki version 2013. According to resolution 008430/1993 from Colombia's Ministry of Health, this is constituted as a study without risk, so informed consent was not required, as it is considered that this article does not contain personal information that allows to identify the patients.

Results

Baseline demographics and clinical characteristics

From a cohort of 467 patients with psoriasis, 12.2% ($n = 57$) achieved the dose tapering inclusion criteria (Fig. 1). The global and dose tapering baseline cohort characteristics are shown in Table 1. Following time represented a total of 108 person-years. In the global cohort, 30% ($n = 142$) received adalimumab, 18.2% ($n = 85$) ustekinumab, 15.2% ($n = 71$) secukinumab, 13.9% ($n = 65$) ixekizumab, 8.5% ($n = 40$) guselkumab, 6.4% ($n = 30$) etanercept, 7.2% ($n = 34$) received other agents. All the clinical data was complete and without missing data. In the dose tapering strategy cohort, 65% ($n = 37$) were men, with a median age of 57 years (IQR: 44–66), disease evolution time of 15 years (IQR 10–27), and time in optimization of 8 months (IQR 1.54–13.2). Patients in the dose-tapering group had lower median BMI (27 vs. 25.3), weight (75 vs. 70), and age at diagnosis (34 vs. 32). Also, lower frequencies of tabaquism (11.2% vs. 7.0%), diabetes (13.2% vs. 12.3%), but a higher frequency of hypertension (21.3% vs. 31.6%), as shown in Table 1.

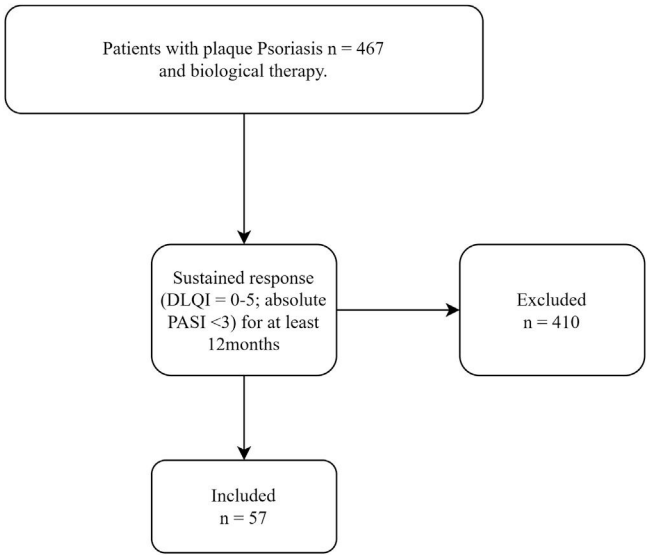

Fig. 1 – Flow chart. Flow chart selection of patients.

Table 1 – Summary of baseline demographics, disease, and clinical variables.

	Global ($n = 467$)	Dose tapering ($n = 57$)
Variable		
Men	322 (63.4%)	37 (64.9%)
Age, years*	52 (41–62)	57 (44–66)
Weight, kg*	75 (69–80)	70 (63–76)
Height, cm*	166 (159–172)	165 (160–170)
BMI, kg/m^2*	27 (24–29)	25.3 (24.1–27.8)
More than 3 years in the program	211 (41.5%)	2 (3.5%)
History of diabetes	67 (13.2%)	7 (12.3%)
Cardiovascular disease	68 (13.4%)	15 (26.3%)
Hypertension	108 (21.3%)	18 (31.6%)
DLQI >10	190 (37.4%)	5 (8.8%)
Tabaquism	57 (11.2%)	4 (7.0%)
Chronic renal disease	25 (4.9%)	5 (8.8%)
Age at diagnosis	34 (22–44)	32 (21–47)
Psoraisis duration*	12 (7–23)	15 (10–27)
PASI at admission to the program*	4 (1.0–7.2)	2.2 (1.3–2.5)
Treatment time, years	4 (2.9–6.9)	2 (1.7–3)
Age group 1		
12–17 years	1 (0.2%)	0 (0%)
18–28 years	19 (3.7%)	(1.8%)
29–59 years	332 (65.4%)	33 (57.9%)
>60 years	156 (30.7%)	23 (40.4%)
Biologic therapy		
Adalimumab	30% ($n = 142$)	35% (20)
Ustekinumab	18.2% ($n = 85$)	24.5% (14)
Secukinumab	15.2% ($n = 71$)	15.8% (9)
Ixekizumab	13.9% ($n = 65$)	14% (8)
Guselkumab	8.5% ($n = 40$)	5.2% (3)
Etanercept	6.4% ($n = 30$)	5.2% (3)
Other	7.3% ($n = 34$)	

* Median and IQR.

Table 2 – Characteristics of optimization strategy.

Dose tapering strategy				
Increase in dose interval	48 (84.2%)			
Decrease dose	9 (15.8%)			
Optimization strategy by drug/molecule from the global cohort ($n = 467$)	Total	Increase in dose interval, *n* (%)	Decrease dose, *n* (%)	Person year
Ustekinumab	16.4% (14/85)	13 (27.1)	1 (11.1)	23
Adalimumab	14% (20/142)	20 (41.7)	0	35
Secukinumab	12.6% (9/71)	1 (2.1)	8 (88.9)	13
Ixekizumab	12.3% (8/65)	8 (16.7)	0	9
Etanercept	10% (3/30)	3 (6.2)	0	5
Guselkumab	7.5% (3/40)	3 (6.2)	0	3

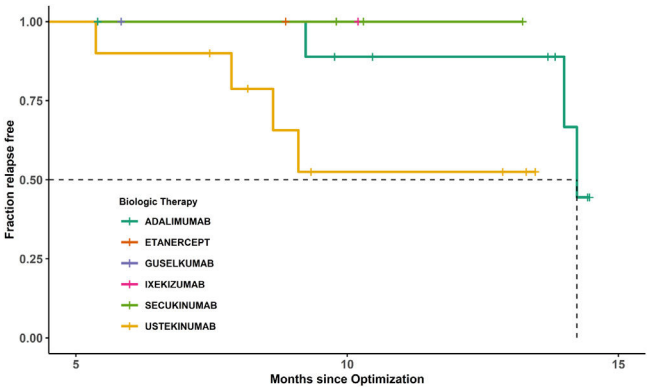

Fig. 2 – Kaplan–Meier, relapse probability in patients under optimization strategy. Kaplan–Meier, the proportion of patients without relapse.

Outcome

The optimization strategy was 85.8% due to an increase in the application interval and 14.2% due to a dose decrease; all the biological therapies had a similar frequency of optimization, although Guselkumab was the least optimized (Table 2). Although 12% (7 patients) relapsed, the incidence rate was 7.4 for 100 person-years (95% CI 3.44–14). Three patients and five patients, at a median time of 14 and 8 months, relapsed with adalimumab and ustekinumab, respectively. Those patients restart the previous regimen after achieving clearance (Fig. 2).

Discussion

All major pivotal studies focus on clearance and safety and do not involve dose reduction or discontinuation of biological therapy.[4] Although, there is an ongoing randomized non-inferiority clinical trial, the current data comes from registries that reported reduced doses without decreasing efficacy.[13] The most frequent inclusion criteria for dose tapering in non-clinical trial psoriasis registries were therapeutic clearance at PASI and maintaining a PASI value, which are similar to the present study definitions. In this regard, the incidence of 7.4 cases per 100 person-years and 14% of relapse is lower compared with other studies that report 40% relapses in patients with previous clearances.[11] It is also low compared with the 67.7% with 300 mg and 52.4% with 150 mg of the secukinumab retreatment-as-needed strategy relapse rate.[5,14,15] Unfortunately, the following time was short and do not bring up long-term results data. Another limitation of the current data is its focus on anti-TNF, ustekinumab, and secukinumab.[9,16] This study extended the focus and also included ixekizumab and guselkumab.

At the moment, no dose tapering clinical trials in dermatology is available. A rheumatology consensus recommended reducing the dose or interval between 20 and 50% of the regular dose depending on the drug and patient characteristics.[17,18] 20–50% of patients in psoriasis registries under biologic treatment were receiving a reduced dose,[9] but in the present study, it was lower (14%). The patients who started the dose-tapering protocol usually begin after 5 years of treatment[19]; however, in our data only 3% of the patient had more than 3 years in the program. The tendency was to start early the dose tapering strategy and it included anti-IL17 and anti-IL23 therapy.

Obesity, rapid attainment of PASI 100,[11,18] and specific treatment gene polymorphism[20] are prognostic factors associated with psoriasis relapse; this is consistent with our findings and other studies that reported better outcomes in patients with a lower BMI and lower weight when treated with dose-tapering. In our cohort, patients with dose tapering had a lower BMI compared to the non-tapered group (Table 1). The patients who relapsed went back to the previous therapy regimen without any adverse events, which is consistent with other studies.[5,9,16]

Many aspects of the dose-tapping strategy are still unknown. The optimal duration of the dose tapering strategy is unclear with the current data, however, a second step in reducing the dose has been reported.[16] Prognostic models for the prediction of relapse based on unbiased factors and cost-utility studies that determine the impact of dose-tapering strategies in the health system are needed to close the gap between clinical practice and public health in psoriasis. The generalizability of this dose-tapering program is low because it reflects our clinical practice and demographics; further studies are needed to confirm and build a stronger approach.[20]

Conclusions

Most patients in the optimization strategy remain in sustained clinical response after 8 months. The low relapse rates reported in this study support the optimization strategy as effective and without adverse events. Further studies are

needed to improve the dose-tapering strategy to reduce drug exposure, adverse events, and costs to the health system and increase effectiveness, quality of life, and patient compliance.

Funding

Medicarte.

Conflict of interest

None declared.

Supplementary material

The Spanish translation of this article is available as supplementary material.

REFERENCES

1. Bilal J, Berlinberg A, Bhattacharjee S, Trost J, Riaz IB, Kurtzman DJB. Systematic review and meta-analysis of the efficacy and safety of the interleukin (IL)-12/23 and IL-17 inhibitors ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab and tildrakizumab for the treatment of moderate to severe plaque psoriasis. J Dermatolog Treat. 2018;29:569–78, http://dx.doi.org/10.1080/09546634.2017.1422591.
2. Takeshita J, Gelfand JM, Li P, Pinto L, Yu X, Rao P, et al. Psoriasis in the US Medicare population: prevalence, treatment, and factors associated with biologic use. J Invest Dermatol. 2015;135:2955–63, http://dx.doi.org/10.1038/jid.2015.296.
3. Rencz F, Kemény L, Gajdácsi JZ, Owczarek W, Arenberger P, Tiplica GS, et al. Use of biologics for psoriasis in Central and Eastern European countries. J Eur Acad Dermatol Venereol. 2015;29:2222–30, http://dx.doi.org/10.1111/jdv.13222.
4. Armstrong AW, Puig L, Joshi A, Skup M, Williams D, Li J, et al. Comparison of biologics and oral treatments for plaque psoriasis: a meta-analysis. JAMA Dermatol. 2020;156:258–69, http://dx.doi.org/10.1001/jamadermatol.2019.4029.
5. Al-Hammadi A, Ruszczak Z, Magariños G, Chu CY, El Dershaby Y, Tarcha N. Intermittent use of biologic agents for the treatment of psoriasis in adults. J Eur Acad Dermatol Venereol. 2021;35:360–7, http://dx.doi.org/10.1111/jdv.16803.
6. Kamata M, Tada Y. Safety of biologics in psoriasis: review of long-term safety data. J Dermatol. 2018;45:279–86, http://dx.doi.org/10.1111/1346-8138.14096.
7. Mansouri Y, Goldenberg G. Biologic safety in psoriasis: review of long-term safety data. J Clin Aesthet Dermatol. 2015;8:30–42.
8. Spandonaro F, Ayala F, Berardesca E, Chimenti S, Girolomoni G, Martini P, et al. The cost effectiveness of biologic therapy for the treatment of chronic plaque psoriasis in real practice settings in Italy. Bio Drugs. 2014;28:285–95, http://dx.doi.org/10.1007/s40259-014-0084-3.
9. Gambardella A, Licata G, Sohrt A. Dose adjustment of biologic treatments for moderate-to-severe plaque psoriasis in the real world: a systematic review. Dermatol Ther (Heidelb). 2021;11:1141–56, http://dx.doi.org/10.1007/s13555-021-00559-z.
10. Shi L, Lian N, Liu L, Chen M. Tapering and discontinuation of systemic medications in psoriasis patients with low disease activity. Dermatol Ther. 2020;33, http://dx.doi.org/10.1111/dth.13599.
11. Hansel K, Bianchi L, Lanza F, Bini V, Stingeni L. Adalimumab dose tapering in psoriasis: predictive factors for maintenance of complete clearance. Acta Derm Venereol. 2017;97:346–50, http://dx.doi.org/10.2340/00015555-2571.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7, http://dx.doi.org/10.1016/S0140-6736(07)61602-X.
13. Llamas-Velasco M, Daudén E. Reduced doses of biological therapies in psoriasis may increase efficiency without decreasing drug survival. Dermatol Ther. 2020;33:e14134, http://dx.doi.org/10.1111/dth.14134.
14. Gordon KB, Armstrong AW, Foley P, Song M, Shen YK, Li S, et al. Guselkumab efficacy after withdrawal is associated with suppression of serum IL-23-regulated IL-17 and IL-22 in psoriasis: VOYAGE 2 study. J Invest Dermatol. 2019;139, http://dx.doi.org/10.1016/j.jid.2019.05.016, 2437–2446.e1.
15. Blauvelt A, Leonardi CL, Gooderham M, Papp KA, Philipp S, Wu JJ, et al. Efficacy and safety of continuous risankizumab therapy vs treatment withdrawal in patients with moderate to severe plaque psoriasis: a phase 3 randomized clinical trial. JAMA Dermatol. 2020;156:649–58, http://dx.doi.org/10.1001/jamadermatol.2020.0723.
16. Esposito M, Gisondi P, Conti A, Giunta A, Del Giglio M, Di Mercurio M, et al. Dose adjustment of biologic therapies for psoriasis in dermatological practice: a retrospective study. J Eur Acad Dermatol Venereol. 2017;31:863–9, http://dx.doi.org/10.1111/jdv.14145.
17. González-Álvaro I, Martínez-Fernández C, Dorantes-Calderón B, García-Vicuña R, Hernández-Cruz B, Herrero-Ambrosio A, et al. Spanish rheumatology society and hospital pharmacy society consensus on recommendations for biologics optimization in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. Rheumatology. 2015;54:1200–9, http://dx.doi.org/10.1093/rheumatology/keu461.
18. van der Schoot LS, van den Reek JMPA, Grine L, Schots L, Kievit W, Lambert JLW, et al. Dose reduction of the new generation biologics (IL-17 and IL-23 inhibitors) in psoriasis: study protocol for an international, pragmatic, multicenter, randomized, controlled, non-inferiority study-the BeNeBio study. Trials. 2021;22:707, http://dx.doi.org/10.1186/s13063-021-05681-z.
19. Feldman SR, Zhao Y, Navaratnam P, Friedman HS, Lu J, Tran MH. Patterns of medication utilization and costs associated with the use of etanercept, adalimumab, and ustekinumab in the management of moderate-to-severe psoriasis. J Manag Care Spec Pharm. 2015;21:201–9, http://dx.doi.org/10.18553/jmcp.2015.21.3.201.
20. Ovejero-Benito MC, Muñoz-Aceituno E, Sabador D, Reolid A, Llamas-Velasco M, Prieto-Pérez R, et al. Polymorphisms associated with optimization of biological therapy through drug dose reduction in moderate-to-severe psoriasis. J Eur Acad Dermatol Venereol. 2020;34:e271–5, http://dx.doi.org/10.1111/jdv.16256.