Failure of Biologic Therapy in Psoriasis

Rocío Cardona, MD; Natalia M. Pelet del Toro, BS;
Eduardo Michelen-Gómez, BS; Gabriel E. Arias Berríos, MD;
Rafael F. Martín-García, MD

Objective: This study aims to describe the frequency of biologic therapy failure in psoriasis patients along with associated patient demographics and characteristics.

Methods: This was a retrospective medical-record review of psoriasis patients evaluated from January 1st, 2013, through May 1st, 2018, and who failed at least once to adhere to their biologic therapy.

Results: Seventy-seven patients with psoriasis who had discontinued biologic therapy at least once were included in this study. Hypertension (58.4%), diabetes (37.7%), dyslipidemia (27.3%), and psoriatic arthritis (23.4%) were the main comorbidities observed. Adalimumab (ADA, 80.5%), ustekinumab (UST, 70.1%), and etanercept (ETA, 14.2%) were the most frequently used biologics in our cohort. The biologic with the longest mean duration of use prior to its discontinuation was UST (17.0 months), followed by ADA (15.9 months) and ETA (13.6 months).

Conclusion: The most common reason for discontinuing biologic therapy was that said therapy was not effective, though for ETA and UST, the fact that biologic therapies are not universally covered by insurance company was found to be associated with their discontinuation, as well. There were no statistically significant associations found between biologic therapy discontinuation and age, gender, or comorbidities, which last included obesity, class I. Larger studies are warranted to identify risk factors associated with biologic therapy failure to help guide drug selection, decrease morbidity associated with such nonadherence and improve patient outcomes. [*P R Health Sci J 2021;40:63-67*]

Key words: Psoriasis, Biologic therapy, Biologic switching, Biologic therapy failure, Biologic therapy discontinuation

Many advances regarding biologic drugs for the treatment of psoriasis have been made, although the discontinuation of these agents (because of inefficacy, side effects, the fact that biologic therapies are not universally covered by insurance companies, and/or patient preference) continues to be reported (1, 2, 3, 4). Biologic switching, the discontinuation of one biologic to transition to another, has been reported to be as high as 44.1% (2).

The main reason that psoriasis patients give for discontinuing their biologic therapy is the ineffectiveness of that treatment (3, 5). Correspondingly, Gniadecki et al confirmed that a biologic's efficacy decreases over time (6). Drug survival, or time to the discontinuation of a drug, is determined by a given medication's efficacy and safety profile, as well as by other factors (7). The average drug survival of a biologic is estimated to be 5 years (5, 8). Body mass index (BMI) (4), biologic immunogenicity (9, 10), and alcohol and tobacco use (11) have all been associated with treatment inefficacy and subsequent biologic therapy discontinuation. Likewise, some studies have found that being female predisposes such patients to developing side effects that compromise drug survival (4). The goal of this study was to identify patient's characteristics that could serve as predictors for the discontinuation of biologic therapy. To improve treatment outcomes and decrease morbidity in patients with psoriasis, it is important to detect those who are at risk of biologic therapy failure.

Patients and methods

Data extraction

Following its approval by the institutional review board of the University of Puerto Rico School of Medicine (protocol no. B1340218), a retrospective, electronic medical-record (EMR) review at the University of Puerto Rico School of Medicine Dermatology Clinics was conducted. This study included patients 18 years of age or older with a diagnosis of psoriasis

School of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico

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Address correspondence to: Rocío M. Cardona, MD, University of Puerto Rico School of Medicine, Department of Dermatology, PO Box 365067, San Juan, PR 00936-5067. Email: rociomcardona@gmail.com

who had failed biologic therapy at least once and who had been evaluated from January 1st, 2013, through May 1st, 2018. The data collected included age, gender, BMI, comorbidities, social history (including whether the patient actively used alcohol or tobacco during his or her treatment with a biologic agent), treatment duration, and the reasons for biologic therapy discontinuation (inefficacy, side effects, insurance issues, or other). Certain phrases on medical records indicated a corresponding lack of efficacy. Evaluating physicians generated such comments on EMR assessments as "lack of improvement" and "refractory lesions," which comments were seen as being related to the eventual termination of therapy. The duration of therapy is reported in consecutive months of use; therefore, the length of time of therapy prior to an interruption of more than 3 months in that therapy was not included in treatment duration, which is similar to what has been done in other trials (3, 4). Patients not on biologic therapy for their psoriasis or those who had not discontinued biologic therapy were excluded. A total of 537 patients with a diagnosis of psoriasis were identified as a result of the retrospective medical-record review.

After applying the exclusion and inclusion criteria (Figure 1) to the records, the study personnel analyzed the data of those that remained, all of which were of individuals who had discontinued therapy (n = 77).

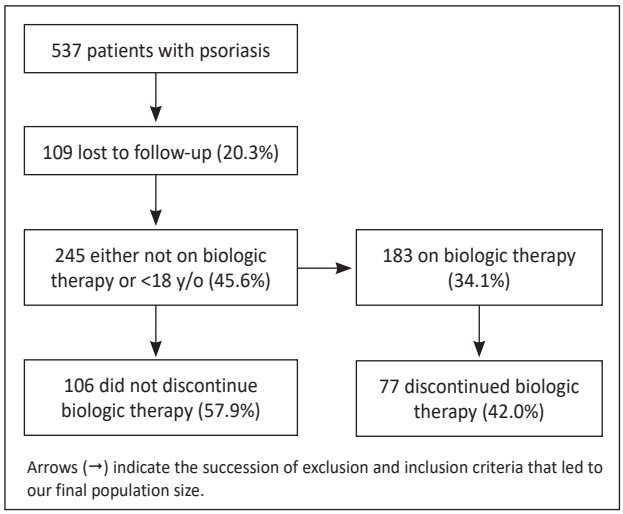

Figure 1. Inclusion and exclusion criteria

Statistical analysis

A descriptive analysis was conducted, and categorical data were summarized as frequencies with percentages, while continuous data were summarized with measures of central tendency and dispersion (frequency, mean ±SD, median, minimum, and maximum values). A comparison of proportion between groups was performed (Fisher's exact test); a mean comparison was performed using a t-test. All the statistical analyses were evaluated with a 2-tailed significance level of .05. Statistical analysis was performed using STATA software, v. 14.0.

Results

A mean age of 49.7 years was observed, with a female majority of 63.6% (n = 49) having been identified. An age-quartile analysis revealed that the majority of the patients were from 36 to 50 years old (n = 25; 32.5%) or 51 to 65 years old (n = 26; 33.8%), with the remaining patients distributed evenly between the age groups of 18 to 35 and over 65 years of age (n = 13 [16.9%] for both age groups). Hypertension (58.4%), diabetes (37.7%), dyslipidemia (27.3%), and psoriatic arthritis (PsoA, 23.4%) were the main comorbidities observed (Table I). Social histories and BMI scores were available for 45 of the 77 patients included in this cohort. Active alcohol or tobacco use during biologic therapy was noted in 6.7% and 4.4% of the participants, respectively. The mean BMI was 32.6 kg/m^2, and most of the patients were found to suffer from obesity, class I (42.2%), or overweight (22.2%), as demonstrated in Table 1.

Table 1. Patient comorbidities and body mass index scores

Characteristics	N (%)
Past medical history	
HTN	45 (58.4)
DM2	29 (37.7)
Dyslipidemia	21 (27.3)
PsoA	18 (23.4)
CAD	5 (6.5)
MDD	5 (6.5)
Anxiety	4 (5.2)
BMI (kg/m^2)	
Normal (18.5–24.9)	7 (15.6)
Overweight (25.0–29.9)	10 (22.2)
Obese, class I (30.0–34.9)	19 (42.2)
Obese, class II (35.0–39.9)	4 (8.9)
Obese, class III (>40)	5 (11.1)

HTN: hypertension; DM2: diabetes mellitus, type II; PsoA: psoriatic arthritis; CAD: coronary artery disease; MDD: major depressive disorder; BMI: body mass index.

Table 2 depicts the frequency of biologic therapy use and discontinuation as well as the mean duration of therapy. Adalimumab (ADA), ustekinumab (UST), and etanercept (ETA) were the most frequently used (80.5%, 70.1%, and 14.2%, respectively) biologics. The biologic with the longest mean duration prior to discontinuation was UST (17.0 months), followed by ADA (15.9 months) and ETA (13.6 months). The most discontinued biologics were ADA (77.4%), ETA (72.7%), and UST (59.3%). Table IV details the reasons for discontinuation, with inefficacy being the most common for all the biologic groups, followed by the fact that a given biologic therapy was not covered by the insurance company of a given patient. The side effects leading to biologic therapy discontinuation are depicted in Table 3, along with other reasons for ceasing biologic therapy. During the retrospective EMR review, reasons classified under the umbrella term "side effects" were able to be associated directly with biologic use,

whereas those classified under the umbrella term "other" were not. There was no significant pattern identified with the reported side effects associated with the discontinuation of biologic treatment.

Age, gender, BMI, and comorbidities were not associated with the discontinuation of ADA, ETA, or UST ($P > .05$). Similarly, Table 4 demonstrates the statistically significant association between inefficacy and the discontinuation of ADA, UST, and ETA ($P < .001$), while the lack of insurance coverage for the 2 relevant biologic therapies was significantly associated with the discontinuation of UST ($P < .001$) and ETA ($P = .001$).

Table 2. Frequency of biologic therapy use and discontinuation with mean duration of therapy

Biologic therapy	On biologic therapy n (%)	Biologic duration (mean months + sd)	Biologic therapy discontinuation (%)
Adalimumab	62 (80.5)	15.9 + 13.5	48 (77.4)
Ustekinumab	54 (70.1)	17.0 + 14.0	32 (59.3)
Etanercept	11 (14.2)	13.6 + 5.9	8 (72.7)
Secukinumab	5 (6.5)	8.8 + 5.3	1 (20.0)
Ixekizumab	5 (6.5)	7.8 + 5.4	1 (20.0)
Infliximab	2 (2.6)	8.5 + 5.0	2 (100.0)
Guselkumab	1 (13.0)	2.0 + 0.0	0 (0.0)

SD: standard deviation.

Table 3. Side effects leading to biologic therapy discontinuation

Discontinued biologic	Side effect	Other
Adalimumab	3 total: 2 injection-site reactions 1 papular/pulmonary sarcoidosis	6 total: 2 patient preference 1 thyroid cancer 1 URTI 2 transaminitis
Ustekinumab	3 total: 1 chest pain/fatigue 1 weakness/fatigue 1 pruritic skin rash/lip edema	4 total: 1 RCC 2 patient preference 1 rheumatology switched biologic
Etanercept	0 total	1 total: 1 arrhythmia

URTI: upper respiratory tract infection; RCC: renal cell carcinoma

Table 4. Association of biologic therapy discontinuation and inefficacy, lack of insurance coverage, side effects, and other.

Discontinued biologic	Inefficacy (%)	P value	SE (%)	P value	Insurance (%)	P value	Other (%)	P value
Adalimumab (n = 48)	37 (77.1)	<.001	3 (6.3)	.286	2 (4.2)	.524	6 (12.5)	.078
Ustekinumab (n = 8)	14 (43.8)	<.001	3 (9.4)	.068	10 (31.3)	<.001	4 (12.5)	.027
Etanercept (n = 8)	4 (50.0)	<.001	0 (0.0)	-	3 (37.5)	.001	1 (12.5)	.104

SE: side effects

Discussion

Our data describe the demographics and comorbidities of psoriasis patients who discontinued biologic therapy at least once. This group had a mean age of 49.7 years, with a female predominance (63.6%) and an average BMI of 32.6 kg/m^2, with most of the participants having been found to suffer from obesity, class I (42.2%), or overweight (22.2%), which is very similar to what was found by Kimball et al in their multi-center, prospective registry of psoriasis patients who were on, or were candidates to receive, systemic or biologic therapy (12). Our population had increased frequencies of hypertension, type II diabetes, dyslipidemia, and PsoA compared to Kimball et al's cohort; CAD, which may have been underreported in our cohort, was the exception to this tendency to increased frequencies (12). Heiss et al also noted an increased frequency of comorbidities associated with cardiac disease in Hispanics compared to Caucasians, which highlights the importance of reinforcing healthy lifestyle choices (e.g., diet and exercise, consulting a nutritionist), as well as of performing adequate follow-up and managing comorbidities in Hispanics with psoriasis (13).

No significant association between biologic therapy discontinuation and age, gender, comorbidities, or BMI was found in our cohort. Reddy et al observed increased drug survival (time to discontinuation) in those with PsoA, while Warren et al did not find any such association between PsoA and drug survival (3, 14). Having a BMI above 35, being an active smoker, and using ETA have been associated with inefficacy, while being female and using infliximab have been associated with adverse events (3). Increased age and a high BMI have been associated with the inefficacy of TNF-alpha inhibitors (TNFIs) (15, 16, 17). Regarding the predictors of biologic therapy discontinuation, Zweegers et al noted that women who used ADA and ETA tended to suffer from more side effects than did male patients and that the therapies of individuals with high BMIs who used ETA and UST tended to be inefficacious compared to the therapies of those with lower BMIS (4). Honda et al found higher baseline Psoriasis Area and Severity Index (PASI) scores with increasing age and an association between a high baseline PASI and overall biologic therapy discontinuation, although they did not find any significant associations between either UST or infliximab discontinuation with age, gender, baseline PASI, or smoking (2). Active smoking and/or alcohol use during biologic therapy can potentially decrease treatment efficacy in psoriasis by exacerbating the underlying disease (11).

In our cohort, ADA is the most prescribed biologic (80.5%), followed by UST (70.1%) and ETA (14.2%), while the most discontinued is ADA (77.4%), followed by ETA (72.7%) and

UST (59.3%). Warren et al also noted that there was a majority of patients on ADA (53%), with more PsoA cases on TNFIs than UST (3). The discontinuation of biologic therapy was observed in 42% of our patients with psoriasis, and treatment inefficacy was the most common reason that was statistically significant for ADA, UST, and ETA. Similarly, inefficacy (74.5%), followed by adverse events (21.6%), was the principal reason for biologic switching in a study conducted by Honda et al (2). Other authors have observed that ADA and UST are associated with primary failure (inefficacy noted since the initiation of therapy), while infliximab is associated with secondary failure (initial improvement followed by inefficacy) and infusion-site reactions (3, 19). A trend in terms of side effects leading to the discontinuation of biologic therapy was not found in our cohort, although Zweegers et al found an increased frequency of side effects with the use of ETA (51%), followed by ADA (38%) and then UST (11%) with infections (mostly upper respiratory tract in origin) leading primarily to the discontinuation of ADA and ETA but not UST (4). In our study, the fact that biologic therapies are not universally covered by insurance companies was also significantly associated with the discontinuation of ETA and UST. Some authors have opined that the costs associated with biologic therapy may be one of the reasons that patient terminate biologic treatment (1).

In our cohort, UST had the longest mean duration of therapy (17 months) prior to its discontinuation; it was followed by ADA (15.9 months) and ETA (13.6 months). Superior drug survival with UST (compared to other biologic agents) has been reported in other studies (3, 4). Regarding efficacy and side effects, previous studies have reported a higher drug survival in the UST group compared to the ADA and ETA groups after correcting for confounders, while no significant difference was found between the ADA and the ETA groups (4). However, ADA has demonstrated the lengthiest drug survival within the TNFI group (3).

The superior drug survival rate of UST compared to those rates of TNFIs can be explained by its increased efficacy (20), decreased immunogenicity (21), and adequate side-effect profile, as well as the fact that it tends to be preferred by patients because of the decreased dosing regimen and its method of administration (3). Differences in clinical presentation, prognosis, communication of symptoms, and treatment outcomes have been proposed as possible explanations for females being associated with side effects leading to premature termination of therapy (22). Immunogenicity can lead to the decreased efficacy of biologic therapy with time and has been reported to be as high as 19.5 to 51.5% for infliximab, 4 to 46% for ADA, 1.1 to 18.3% for ETA, and 3.8 to 5.1% for UST (21). Chimeric molecules such as infliximab contain murine portions and are more immunogenic than are other humanized antibodies (ADA, UST, and ETA, for example) (23, 24,25).

This study is limited by its retrospective nature; therefore, it is subject to recall bias as well as reporting bias. Overall, the EMR assessments did not make consistent use of objective measures, such as change from baseline in the percentage of body surface area involvement or PASI scores, to determine treatment efficacy. This study is limited by the subjective nature of determining biologic therapy failure based on physician and patient appraisals of treatment response. In addition, it is a small sample size, subject to selection bias as well as referral bias since the study population came from a single, tertiary center. Additional studies should compare psoriasis patients who required a change in biologic therapy versus those who did not and compare, as well, the drug survival rates of the available biologic therapies and focus on larger, prospective studies to determine the impact of a given patient's characteristics on his or her decision to discontinue biologic therapy. Lastly, patients can be less forthcoming about tobacco (18) and/or alcohol use during clinical encounters, which could explain the low frequencies of alcohol and tobacco use reported in our cohort.

Conclusion

Biologic inefficacy was identified as the most common reason for discontinuing biologic therapy in all drug groups and was statistically significant for ADA, UST, and ETA. Nonetheless, no statistically significant associations were found between biologic therapy discontinuation and age, BMI, gender, or comorbidities, while the lack of coverage by some insurance companies was significantly associated with the discontinuation of ETA and UST. The identification of patient characteristics as potential risk factors for premature biologic therapy discontinuation may decrease morbidity associated with biologic therapy failure in psoriasis patients and improve clinical outcomes.

Resumen

Objetivo: El objetivo es describir la frecuencia de la descontinuación de terapia biológica en pacientes con psoriasis y las características asociadas al fallo del tratamiento. Métodos: Una revisión retrospectiva de los récords médicos de pacientes con psoriasis evaluados entre el 1 de enero del 2013 y el 1 de mayo del 2018 que fallaron tratamiento con biológicos al menos una vez. Resultados: Setenta y siete pacientes con psoriasis que descontinuaron terapia con biológicos fueron incluidos. Se describió la prevalencia de hipertensión (58.4%), diabetes (37.7%), dislipidemia (27.3%) y artritis psoriásica (23.4%). Adalimumab (ADA, 80.5%), Ustekinumab (UST, 70.1%) and Etanercept (ETA, 14.2%) fueron los biológicos más utilizados. El biológico con mayor tiempo de uso fue UST (17 meses), seguido por ADA (15.9 meses) y ETA (13.6 meses). Conclusión: Factores como la ineficacia del tratamiento biológico y la falta de cubierta de plan médico se asociaron al fallo terapéutico con biológicos en la cohorte. No hubo asociación entre la edad, género o comorbilidades del paciente y la descontinuación de terapia biológica. Se necesitan estudios de poblaciones más grandes para identificar factores de riesgo asociados a la descontinuación de terapia biológica en pacientes con psoriasis.

Esta información podrá guiar la selección de terapia biológica, disminuir la morbilidad asociada a la falla terapéutica y mejorar el pronóstico clínico de pacientes con psoriasis.

References

1. Foster SA, Zhu B, Guo J, et al. Patient Characteristics, Health Care Resource Utilization, and Costs Associated with Treatment-Regimen Failure with Biologics in the Treatment of Psoriasis. J Manag Care Spec Pharm. 2016;22(4):396-405. doi:10.18553/jmcp.2016.22.4.396
2. Honda H, Umezawa Y, Kikuchi S, et al. Switching of biologics in psoriasis: Reasons and results. J Dermatol. 2017;44(9):1015-1019. doi:10.1111/1346-8138.13860
3. Warren RB, Smith CH, Yiu ZZN, et al. Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015;135(11):2632-2640. doi:10.1038/jid.2015.208
4. Zweegers J, van den Reek JM, van de Kerkhof PC, et al. Body mass index predicts discontinuation due to ineffectiveness and female sex predicts discontinuation due to side-effects in patients with psoriasis treated with adalimumab, etanercept or ustekinumab in daily practice: a prospective, comparative, long-term drug-survival study from the BioCAPTURE registry. Br J Dermatol. 2016;175(2):340-347. doi:10.1111/bjd.14552
5. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. Br J Dermatol. 2015;172(1):244-252. doi:10.1111/bjd.13343
6. Gniadecki R, Kragballe K, Dam TN, Skov L. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. Br J Dermatol. 2011;164(5):1091-1096. doi:10.1111/j.1365-2133.2011.10213.x
7. van den Reek JMPA, Kievit W, Gniadecki R, et al. Drug Survival Studies in Dermatology: Principles, Purposes, and Pitfalls. J Invest Dermatol. 2015;135(7):1-5. doi:10.1038/jid.2015.171
8. Menter A, Papp KA, Gooderham M, 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). J Eur Acad Dermatol Venereol. 2016;30(7):1148-1158. doi:10.1111/jdv.13611
9. Vincent FB, Morand EF, Murphy K, Mackay F, Mariette X, Marcelli C. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. Ann Rheum Dis. 2013;72(2):165-178. doi:10.1136/annrheumdis-2012-202545
10. Chaparro M, Guerra I, Muñoz-Linares P, Gisbert JP. Systematic review: antibodies and anti-TNF-α levels in inflammatory bowel disease. Aliment Pharmacol Ther. 2012;35(9):971-986. doi:10.1111/j.1365-2036.2012.05057.x
11. Hayes J, Koo J. Psoriasis: depression, anxiety, smoking, and drinking habits. Dermatol Ther. 2010;23(2):174-180. doi:10.1111/j.1529-8019.2010.01312.x
12. Kimball AB, Leonardi C, Stahle M, et al. Demography, baseline disease characteristics and treatment history of patients with psoriasis enrolled in a multicenter, prospective, disease-based registry (PSOLAR). Br J Dermatol. 2014;171(1):137-147. doi:10.1111/bjd.13013
13. Heiss G, Snyder ML, Teng Y, et al. Prevalence of metabolic syndrome among Hispanics/Latinos of diverse background: the Hispanic Community Health Study/Study of Latinos. Diabetes Care. 2014;37(8):2391-2399. doi:10.2337/dc13-2505
14. Reddy SP, Lin EJ, Shah VV, Wu JJ. Persistence and failure rates of adalimumab monotherapy in biologic-naïve patients with psoriasis: A retrospective study. J Am Acad Dermatol. 2016;74(3):575-577. doi:10.1016/j.jaad.2015.11.005
15. Menter A, Gordon KB, Leonardi CL, Gu Y, Goldblum OM. Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis. J Am Acad Dermatol. 2010;63(3):448-456. doi:10.1016/j.jaad.2009.09.040
16. Di Lernia V, Tasin L, Pellicano R, Zumiani G, Albertini G. Impact of body mass index on retention rates of anti-TNF-alfa drugs in daily practice for psoriasis. J Dermatolog Treat. 2012;23(6):404-409. doi:10.3109/09546634.2011.593489
17. Di Lernia V, Ricci C, Lallas A, Ficarelli E. Clinical predictors of non-response to any tumor necrosis factor (TNF) blockers: a retrospective study. J Dermatolog Treat. 2014;25(1):73-74. doi:10.3109/09546634.2013.800184
18. Burris JL, Studts JL, DeRosa AP, Ostroff JS. Systematic Review of Tobacco Use after Lung or Head/Neck Cancer Diagnosis: Results and Recommendations for Future Research. Cancer Epidemiol Biomarkers Prev. 2015;24(10):1450-1461. doi:10.1158/1055-9965.EPI-15-0257
19. Umezawa Y, Nobeyama Y, Hayashi M, et al. Drug survival rates in patients with psoriasis after treatment with biologics. J Dermatol. 2013;40(12):1008-1013. doi:10.1111/1346-8138.12353
20. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010;362(2):118-128. doi:10.1056/NEJMoa0810652
21. Carrascosa JM, van Doorn MB, Lahfa M, Nestle FO, Jullien D, Prinz JC. Clinical relevance of immunogenicity of biologics in psoriasis: implications for treatment strategies. J Eur Acad Dermatol Venereol. 2014;28(11):1424-1430. doi:10.1111/jdv.12549
22. Teunissen TAM, Rotink ME, Lagro-Janssen ALM. Gender differences in quality of care experiences during hospital stay: A contribution to patient-centered healthcare for both men and women. Patient Educ Couns. 2016;99(4):631-637. doi:10.1016/j.pec.2015.10.033
23. De Groot AS, Terry F, Cousens L, Martin W. Beyond humanization and de-immunization: tolerization as a method for reducing the immunogenicity of biologics. Expert Rev Clin Pharmacol. 2013;6(6):651-662. doi:10.1586/17512433.2013.835698
24. Emi Aikawa N, de Carvalho JF, Artur Almeida Silva C, Bonfá E. Immunogenicity of Anti-TNF-alpha agents in autoimmune diseases. Clin Rev Allergy Immunol. 2010;38(2-3):82-89. doi:10.1007/s12016-009-8140-3
25. Lombardi G, Perego S, Sansoni V, Diani M, Banfi G, Altomare G. Anti-adalimumab antibodies in psoriasis: lack of clinical utility and laboratory evidence. BMJ Open. 2016;6(12):e011941. Published 2016 Dec 9. doi:10.1136/bmjopen-2016-011941