Brief Report

Journal of Psoriasis and Psoriatic Arthritis
2023, Vol. 8(1) 11–18

DOI: 10.1177/24755303221131259
journals.sagepub.com/home/jps


Factors Associated with Multi-Biologic Use in Psoriasis Patients at an Academic Medical Center and Review of Biologic Survival

Edward Hadeler, BA[1], Sugandh Kumar, PhD[1], Samuel Yeroushalmi, BS[1], Julie Hong, BS[1], Elizabeth Wallace, MD[2], George Han, MD, PhD[3], Megan Mosca, BS[1], Erin Bartholomew, BA[1], Mimi Chung, BA[1], Marwa Hakimi, MD[1], Soumya Reddy, MD[4], Jose Scher, MD[4], Tina Bhutani, MD, MAS[1], George Gondo, MA[5], April Armstrong, MD, MPH[6], Stacie Bell, PhD[7], and Wilson Liao, MD[1]

Abstract

Background: Despite their impressive efficacy in phase 3 trials, biologic agents for psoriasis (PsO) may lose efficacy over time. The factors associated with loss of efficacy have yet to be fully elucidated. **Objective:** We aimed to identify factors associated with PsO patients using multiple biologics in comparison to patients who used 1 biologic. We also reviewed the literature comparing the survival of different biologic agents for PsO. **Methods:** We examined clinical data from 222 psoriasis patients at the University of California San Francisco, of whom 51 reported use of 3 or more biologics and of whom 171 reported use of only a single biologic agent at the time of enrollment into a research database from 2006-2020. **This study was IRB-approved at UCSF (#10-02830) and all subjects provided written informed consent.** We performed univariate and multivariate regression analysis to identify significant demographic features, clinical features, and co-morbidities associated with multi-biologic use. We performed a literature review of studies comparing psoriasis biologic survival at 1, 2, and 5 years and factors associated with single biologic failure. **Results:** In univariate analysis, duration of PsO, initial presentation of PsO on the gluteal cleft, erythrodermic psoriasis, and acne were associated with using 3 or more biologics. In multivariate analysis, duration of PsO, erythrodermic psoriasis, and acne remained significant. Our review of biologic survival revealed differences according to biologic class. **Conclusion:** We identified novel factors associated with multi-biologic use in PsO. Further studies in this area are needed to achieve a precision medicine approach.

Keywords

biologic failure, biologic persistence, biologic survival, psoriasis, multi-biologic use

Introduction

Despite the impressive efficacy of biologic agents demonstrated in phase 3 clinical trials for patients with psoriasis, some agents may lose efficacy over time.[1,2] Drug survival, also referred to as drug persistence, is defined as the duration of time a patient remains on a therapy from initiation to discontinuation or last clinical observation.[3] Researchers and clinicians recognize drug survival as an indicator of real-world efficacy for biologic agents.[4-7] Reasons for biologic failure, or discontinuation, can include loss of efficacy, which can be further subcategorized into primary failure, due to lack of initial efficacy, or secondary failure, due to loss of efficacy during the maintenance period.[3] Safety or adverse events can also influence biologic failure and while good

[1]Department of Dermatology, University of California, San Francisco, CA, USA
[2]Department of Dermatology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[3]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[4]New York University Langone Health, New York, NY, USA
[5]National Psoriasis Foundation, Portland, OR, USA
[6]Department of Dermatology, University of Southern California Keck School of Medicine, Los Angeles, CA, USA
[7]Opsis Health/Global Nutrition Project, Golden, CO, USA

Corresponding Author:
Wilson Liao, MD, Department of Dermatology, University of California, 2340 Sutter Street, Box 0808, N426, San Francisco, CA 94143, USA.
Email: wilson.liao@ucsf.edu

efficacy and safety profiles are positively correlated with biologic survival,[8-10] several other factors have been identified as well. These factors include loss to follow-up, decisions on behalf of the patient or physician to end or switch therapies,[3,11,12] reimbursement policies, or therapeutic guidelines.[13] Furthermore, demographic and clinical factors are also beginning to surface as factors associated with failure of specific biologic agents.[3,11] In our study, we aimed to identify clinical and demographic factors associated with patients using and/or failing multiple biologic agents in comparison to patients who were treated with 1 biologic agent. We also reviewed the literature comparing the survival of different biologic agents and identifying factors associated with biologic survival.

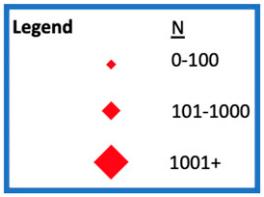
Case-Control Study

We examined clinical data from 222 psoriasis patients at the University of California San Francisco, of whom 51 reported use of 3 or more biologics and of whom 171 reported use of only a single biologic agent at the time of enrollment into a research database from 2006-2020. All patients were confirmed to have a diagnosis of psoriasis by a board-certified dermatologist. Four main dermatology providers at UCSF wrote the biologics prescriptions. The breakdown of biologics used by these 2 groups is shown in Table 1. We analyzed demographic features, clinical features, and self-reported co-morbidities associated with use of 3 or more biologics compared to use of a single biologic.

Factors examined included age, gender, age of psoriasis onset, duration of PsO, body mass index (BMI), smoking status, PsO self-severity according to body surface area estimation, patients' self-reported initial anatomic location of psoriasis, psoriasis subtype, family history, joint pain, medical provider diagnosis of psoriatic arthritis (PsA), co-morbidities, and biologic(s) used. To evaluate differences between groups, we performed univariate regression analysis to identify significant factors associated with multi-biologic use (P-value < .05). We then performed multivariate analysis and included only univariate variables that demonstrated potential for significance (P < .15). Multivariate variables were considered significant if they achieved a P-value of less than .05. In univariate analysis, duration of PsO, initial presentation of PsO on the gluteal cleft, erythrodermic psoriasis, and acne were associated with using 3 or more biologic agents. In multivariate analysis, duration of PsO, erythrodermic psoriasis, and acne remained significant (Table 1). There was a trend towards significance on multivariate analysis (P < .1) for initial presentation of PsO on the gluteal cleft and family history of psoriasis, such that initial presentation on the gluteal cleft was associated with using 3 or more biologic agents and family history was associated with using 1 biologic agent.

Review of Biologic Survival at 1-, 2-, and 5-years

We reviewed the literature to identify studies that compared biologic survival rates across large cohorts of patients. We searched the PubMed database utilizing key search terms such as "*multi-biologic failure*", "*highly refractory psoriasis*", "*causes OR reasons for biologic failure*", "*biologic survival*", and "*biologic persistence*". In an effort to synthesize common outcome information across studies, we identified 5 studies that utilized percentage survival of biologic agents at time points of 1, 2, and 5 years. These studies include single center[12] and multi-center[3,11] retrospective studies and systemic reviews and comparative meta-analyses of multiple studies.[5,13] Biologic agents analyzed include inhibitors for tumor necrosis factor (TNF)-alpha, interleukin (IL)-12/23, IL-17, and IL-23. We compared the 1-, 2-, and 5-year survival rates in these studies across specific biologic agents, emphasizing the weight of each study in evaluating the percent survival of the specific agent by the number of patients evaluated (N). The charts comparing 1-, 2-, and 5-year biologic survival for specific agents are presented in Figures 1-3, respectively. The findings of these studies demonstrate that while all biologic agents have decreased survival over time, certain biologic agents show loss of survival more rapidly than others. At 1-year, biologic agents were demonstrated to have good survival: 70% of patients on TNF-alpha inhibitors survived while 1 study showed only 34% of patients on certolizumab survived at 1 year, however, it should be noted that this study analyzed a small sample (n = 13) of patients on certolizumab.[14] Patients on IL-12/23 and IL-17 inhibitors experienced 1-year biologic survival ranging from 85% to 90%, and IL-23 inhibitors experienced the highest survival at 92% to 96% (Figure 1).



All TNFs = all TNF alpha agents combined.
ADA adalimumab, IFX infliximab, ETA etanercept, CER certolizumab, UST ustekinumab, SEC secukinumab, IXE ixekizumab, BRO brodalumab, TIL tildrakizumab, GUS guselkumab, RIS risankizumab.
The *y*-axis describes the specific class and name of the biologic agent while the *x*-axis describes the percent of patients that survived biologic therapy at the specified time point.

Table 1. Differences in Demographic and Clinic Factors Between Psoriasis Patients on ≥3 Biologics vs Patients on 1 Biologic.

Demographic and Clinical Factors	≥3 Biologics (n = 51)	1 Biologic (n = 171)	Univariate P-value	OR	.95 Confidence Interval	Multivariate P-value	OR	.95 Confidence Interval
Age	46.3 ± 15.6 (n = 51)	43.6 ± 14.3 (n = 170)	.26	1.01	.99-1.03			
Gender (% female)	47.0% female (n = 51)	39.4% female (n = 170)	.33	1.37	.73-2.57			
Age when psoriasis began	23.0 ± 14.5 (n = 51)	24.4 ± 13.9 (n = 170)	.52	.99	.97-1.01			
Duration of PsO in years	**22.9 ± 13.2 (n = 50)**	**19.3 ± 12.6 (n = 168)**	**.05***	**1.02**	**1.0-1.04**	**.05***	**1.03**	**1.00-1.05**
Body mass index	29.47 ± 8.42 (n = 43)	28.10 ± 7.19 (n = 93)	.42	1.02	.97-1.09			
Smoker	4/47 (8.51%)	8/168 (4.76%)	.33	1.86	.48-.62			
PsO self-severity (>10%)	32/51 (62.7%)	96/171 (56.1%)	.40	1.32	.70-2.53			
PsO self-severity (5-10%)	10/51 (19.6%)	51/171 (29.8%)	.15	.57	.26-1.19			
PsO self-severity (1-5%)	5/51 (9.80%)	14/171 (8.19%)	.72	1.22	.38-3.38			
PsO self-severity (<1%)	2/51 (3.92%)	3/171 (1.75%)	.37	1.70	.23-9.00			
Initial: Scalp	19/51 (37.3%)	54/171 (31.6%)	.45	1.29	.66-2.46			
Initial: Ears	9/51 (17.6%)	23/171 (13.5%)	.46	1.38	.57-3.12			
Initial: Elbows/knees	18/51 (35.2%)	46/171 (26.9%)	.25	1.48	.75-2.87			
Initial: Arms/legs	19/51 (37.3%)	49/171 (28.7%)	.24	1.52	.76-2.84			
Initial: Back/stomach/trunk	12/51 (23.5%)	37/171 (21.7%)	.77	1.11	.51-2.29			
Initial: Face	3/51 (5.88%)	14/171 (8.19%)	.59	0.7	.16-2.26			
Initial: Genitals	3/51 (5.88%)	12/171 (7.02%)	.78	.91	.20-3.05			
Initial: Nails	**7/51 (13.7%)**	**12/171 (7.02%)**	**.14**	**2.11**	**.75-5.57**	**.98**	**3.18**	**.83-12.18**
Initial: Palms	3/51 (5.88%)	7/171 (4.09%)	.59	1.46	.31-5.49			
Initial: Soles of feet	1/51 (1.96%)	10/171 (5.85%)	.29	.32	.01-1.74			
Initial: Armpit/groin/folds	5/51 (9.80%)	14/171 (8.19%)	.72	1.22	.38-3.38			
Initial: Gluteal cleft	**8/51 (15.7%)**	**8/171 (4.68%)**	**.01***	**3.79**	**1.32-10.88**	**.09**	**3.18**	**.83-12.18**
Psoriasis type: plaque	45/51 (88.2%)	140/171 (81.9%)	.29	1.66	.69-4.64			
Psoriasis type: guttate	**20/51 (39.2%)**	**45/171 (26.3%)**	**.08**	**1.81**	**.93-3.47**	**.53**	**1.28**	**.59-2.79**
Psoriasis type: pustular	3/51 (5.88%)	11/171 (6.43%)	.89	.91	.20-3.05			
Psoriasis type: erythrodermic	**7/51 (13.7%)**	**5/171 (2.92%)**	**.01***	**5.28**	**1.61-18.6**	**.04***	**4.11**	**1.08-15.73**
Psoriasis type: palm/sole	**5/51 (9.80%)**	**6/171 (3.51%)**	**.08**	**2.99**	**.83-10.04**	**.13**	**3.24**	**.70-14.89**
Psoriasis type: armpits/groin	**7/51 (13.7%)**	**10/171 (5.85%)**	**.07**	**2.56**	**.89-7.06**	**.36**	**1.81**	**.51-6.45**
Family history of psoriasis	**22/51 (43.1%)**	**93/170 (54.7%)**	**.14**	**.62**	**.33-1.16**	**.08**	**.52**	**.25-1.07**
Joint pain/swelling ever	**32/51 (66.7%)**	**91/171 (53.2%)**	**.09**	**1.76**	**.92-3.45**	**.37**	**1.39**	**.67-2.85**
Confirmed PsA Dx	20/51 (39.2%)	54/171 (33.1%)	.35	.82	.55-1.24			
Possible PsA Dx	12/51 (23.5%)	35/171 (21.5%)						
Confirmed or possible PsA Dx	32/51 (62.7%)	89/171 (54.6%)						
High blood pressure	14/51 (27.4%)	55/171 (32.2%)	.52	0.8	.39-1.57			
High cholesterol	10/51 (19.6%)	39/171 (22.8%)	.63	.83	.36-1.75			
High triglycerides	4/51 (7.84%)	10/171 (5.85%)	.61	1.37	.23-1.07			
Coronary artery disease	0/51 (0%)	5/171 (2.92%)	.99	<.01	.01-4.97			
Adult-onset diabetes	4/51 (7.84%)	12/171 (7.02%)	.84	1.13	.61-2.79			
Stroke	2/51 (3.92%)	2/171 (1.17%)	.22	3.45	.30-3.41			
Acne	**5/51 (9.80%)**	**5/171 (2.92%)**	**.05***	**3.60**	**.97-13.50**	**.05***	**4.76**	**1.02-22.20**
Lupus	0/51 (0%)	2/171 (1.17%)	.99	<.01	.01-8.18			

(continued)

Table 1. (continued)

Demographic and Clinical Factors	≥3 Biologics (n = 51)	1 Biologic (n = 171)	Univariate P-value	OR	.95 Confidence Interval	Multivariate P-value	OR	.95 Confidence Interval
Rheumatoid arthritis	3/51 (5.88%)	7/171 (4.09%)	.59	1.46	.31-5.49			
Obesity	**7/51 (13.7%)**	**10/171 (5.85%)**	**.07**	**2.56**	**.88-7.06**	**.80**	**1.19**	**.31-4.60**
Other	12/51 (23.5%)	32/171 (18.7%)	.45	1.34	.61-2.79			
Biologic use								
Etanercept	50/51 (98.0%)	101/171 (59.1%)						
Adalimumab	46/51 (90.2%)	35/171 (20.5%)						
Ustekinumab	23/51 (45.1%)	14/171 (8.19%)						
Alefacept	11/51 (21.5%)	9/171 (5.26%)						
Infliximab	20/51 (39.2%)	7/171 (4.09%)						
Golimumab	1/51 (1.96%)	0/171 (0%)						
Efalizumab	11/51 (21.6%)	4/171 (2.34%)						
Secukinumab	8/51 (15.7%)	1/171 (.58%)						
Ixekizumab	3/51 (5.88%)	0/171 (0%)						
Guselkumab	3/51 (5.88%)	0/171 (0%)						

The following co-morbidities had too low of a frequency for data analysis: Childhood-onset diabetes, dermatomyositis, polymyositis, alopecia areata, Crohn's Disease, ulcerative colitis, Celiac Disease, Sjogren's Disease, multiple sclerosis, Kawasaki Disease, and atopic dermatitis.
Univariate cutoff for inclusion in multivariate model $P < .15$ (shown in bold).
Abbreviations: PsO, Psoriasis; PsA, Psoriatic arthritis.
*Significance cutoff $P < .05$.

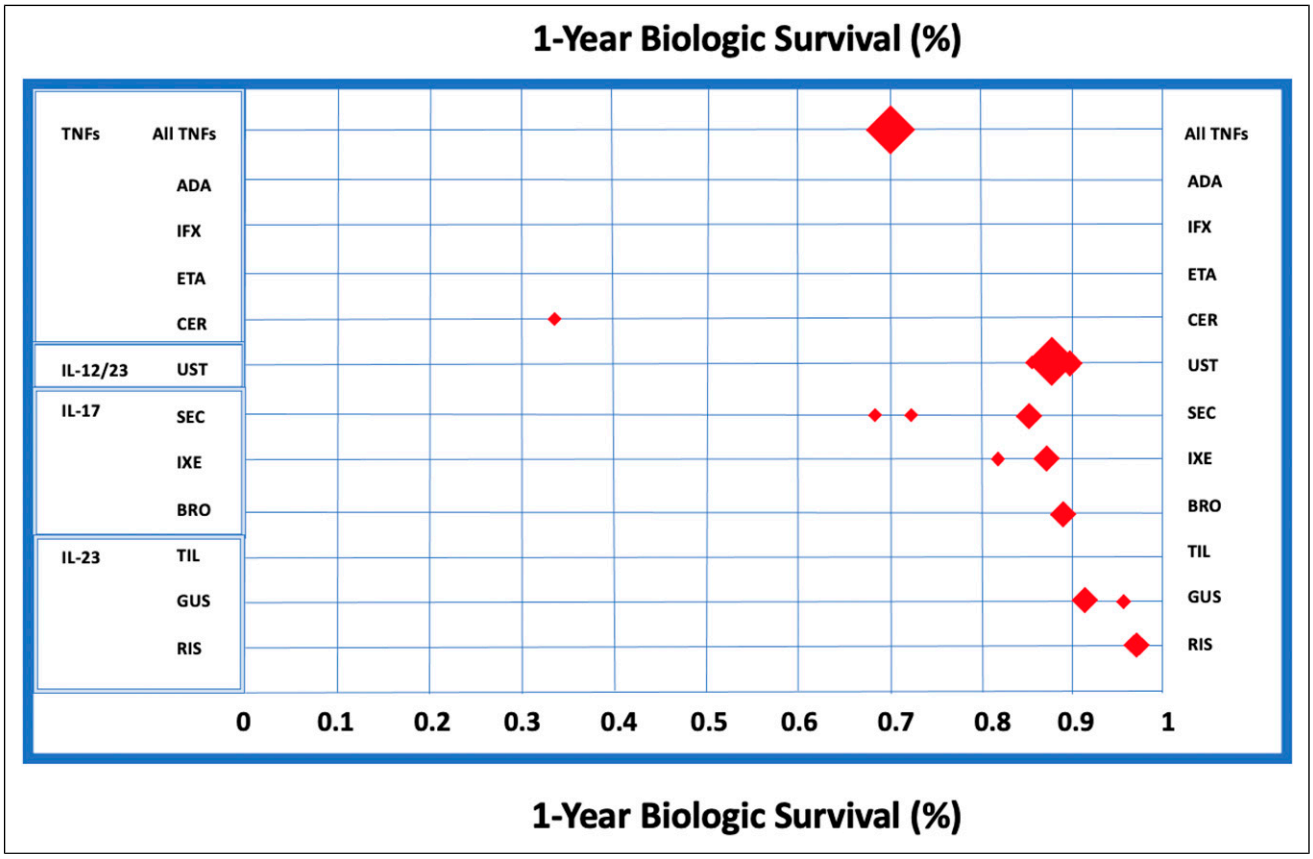


Figure 1. Biologic Survival at 1 Year.

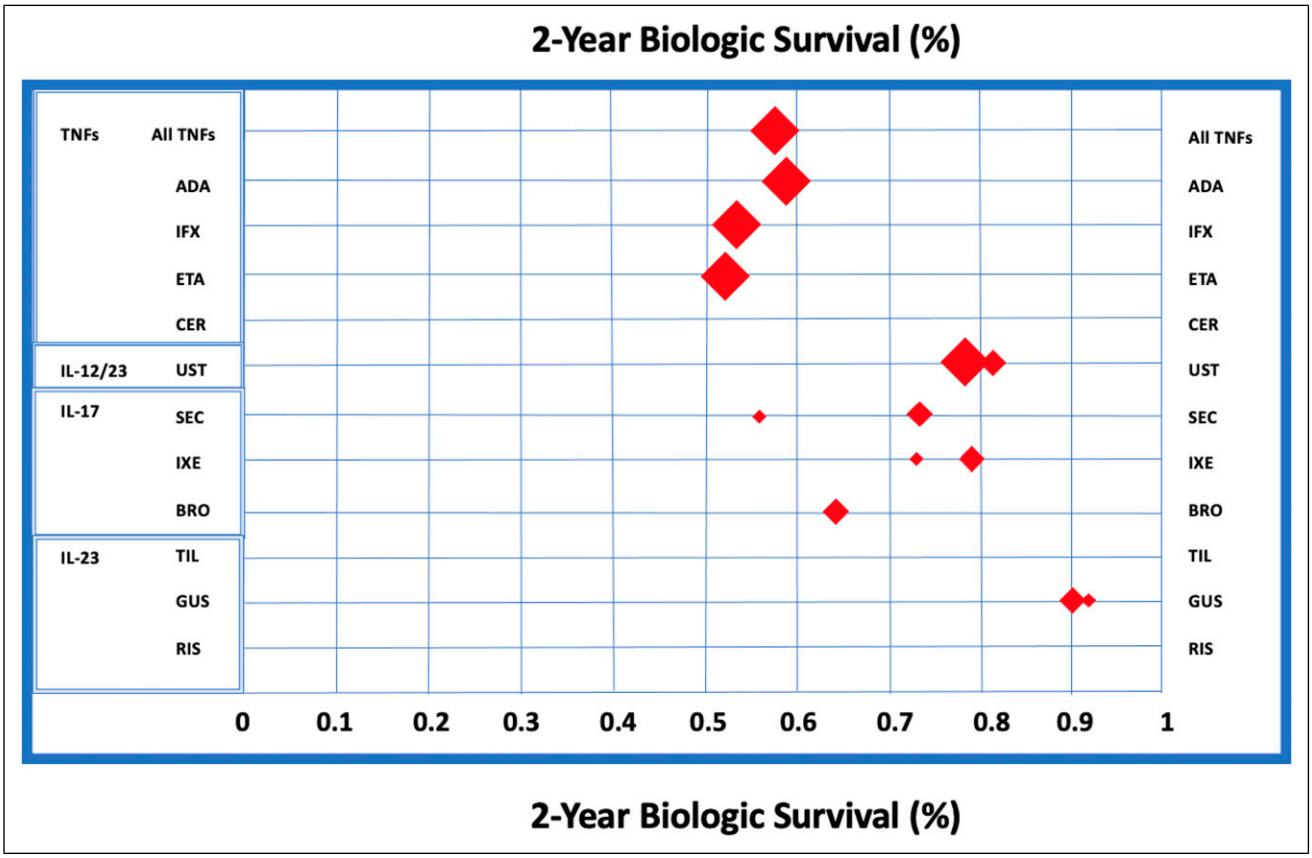


Figure 2. Biologic survival at 2 Years.

Studies assessing biologic failure at 2-years show a similar trend of loss of efficacy across all agents with TNF inhibitors ranging from an estimated 57% to 59%, IL-12/23 inhibitors ranging from 78% to 83%, IL-17 inhibitors ranging from 56% to 79%, and the IL-23 inhibitor, guselkumab ranging from 90% to 92%. Data for 5-year survival was only available for certain TNF-alpha inhibitor (adalimumab, infliximab, and etanercept) and the IL-12/23 inhibitor, ustekinumab. Biologic survival ranged between 35% to 46% for TNF-alpha inhibitors, and 51% for the IL-12/23 inhibitor ustekinumab.

Torres et al also analyzed factors associated with failure of the IL-12/23 inhibitor (ustekinumab), IL-17 inhibitors (secukinumab, ixekizumab, and brodalumab), and IL-23 inhibitors (guselkumab and risankizumab) and found on univariate analysis that body mass index (BMI) greater than 30, weight in kilograms (kg), psoriatic arthritis (PsA), peripherally located PsA, diabetes, previous use of TNF, IL-12/23, IL-17, or IL-23, and number of previous biologics, were all associated with biologic failure. Patients of male sex and who were naïve to systemic or biologic therapy, were less likely to experience biologic failure.[3] On multivariate analysis, they found that BMI was indicative of biologic failure while being naïve to biologic therapy was protective. Utilizing the IL/12-23 inhibitor ustekinumab as a comparator on univariate analysis, they found that the IL-17 agent secukinumab was more likely to experience failure and the IL-23 agent guselkumab was less likely to experience failure.[3] On multivariate analysis, they found that secukinumab was still more likely to experience failure, while risankizumab was protective.[3] On multivariate Cox regression analysis, Kojanova et al looked at factors associated with the failure of the anti-TNF agent, adalimumab, and found that female sex, BMI (30-35), BMI (35-40), psoriasis area severity index (PASI) at treatment start, previous use of 1 biologic agent, previous use of 2 biologic agents, and previous use of 3 or 4 biologic agents, were associated with biologic failure. Interestingly, duration of psoriasis was protective of biologic failure.[11]

Discussion

While previous studies have highlighted clinical and demographic factors associated failure of single agents,[3,11] our study highlights factors associated with using multiple biologic agents. Interestingly, BMI was not associated with greater biologic use in the UCSF cohort, which differs from other study populations analyzing biologic failure of specific agents.[3]

Our study also highlights that patients who present with atypical forms of psoriasis, such as more severe variants of psoriasis like erythrodermic psoriasis, may be more likely to use multiple biologic agents. These variants of psoriasis are often

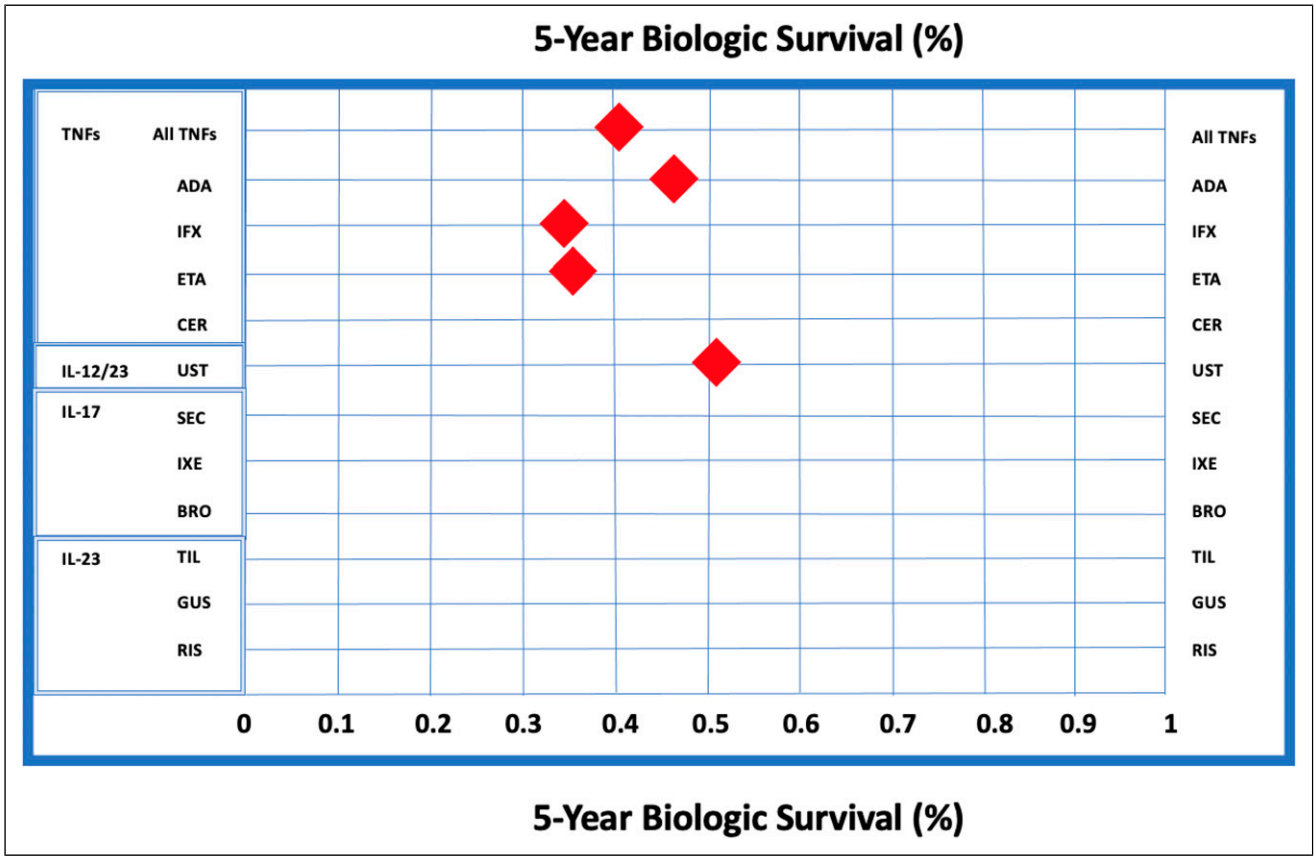


Figure 3. Biologic survival at 5 Years.

difficult to study in the controlled setting and data on the efficacy of biologic agents is limited.[15-18] Further data assessing the efficacy of biologic agents treating these populations is needed.

Interestingly, acne was identified as a significant factor associated with the use of 3 or more biologic agents in our population. Genetic studies of acne have found an association with IL36RN,[19] the same gene associated with pustular psoriasis. As psoriasis may present on a spectrum between autoinflammatory (IL-1, IL-36) to adaptive immunity (IL-17), the presence of acne may suggest an immune response tilted toward the autoinflammatory axis, which could respond less well to current psoriasis biologics. Moreover, the gut microbiome has been linked to several skin diseases[20] such as psoriasis[21] and acne.[22,23] Acne patients may be on oral antibiotic therapy, which may alter the gut microbiome, and there could be a possible link between the gut microbiome and response to biologics, as has been shown in rheumatoid arthritis with response to methotrexate.[24] Further studies identifying a pathogenic link between the gut microbiome and patients who present with acne and psoriasis may strengthen evidence supporting a link between these diseases, identifying additional factors associated with biologic failure. These future studies should also clarify if specific acne treatments (oral antibiotics, isotretinoin, topicals) are associated with multi-biologic failure. It is also possible that acne could be appearing in our study due to other causes. For instance, acne patients may have more concerns about their appearance and higher expectations of medications, so it is important that future studies explore factors such as treatment expectations as well.

There was a trend towards significance for initial presentation of psoriasis on the gluteal cleft. This may demonstrate that the initial presentation of psoriasis on special sites may also predict biologic response. Surprisingly, in the UCSF cohort, the presence of a family history of psoriasis also trended toward significance, such that these patients would more likely use 1 biologic agent compared to 3 or more. This may suggest that the efficacy of biologic agents may differ based on the degree to which a patient's psoriasis manifests due to genetic or environmental factors. Studies have highlighted genetic factors associated with biologic response in psoriasis such as HLA-06:02.[25,26] Previous studies have identified specific environmental antigen exposures linked with psoriasis pathogenesis, especially the guttate subtype.[27-29] The variable prevalence rates of psoriasis across geographic regions,[30] where factors such as distance from the equator, altitude, sunlight exposure, photoprotection habits, and regional variation in antigen exposure can vary,[27] provide further evidence of environmental exposures linked to psoriasis pathogenesis.

Limitations of our study include its cross-sectional design and use of self-reported severity and co-morbidities. While our database captured the number of agents patients have used, each patient completed the questionnaire at varying timepoints in their disease and treatment course. Another limitation was the sample size. There were many trends observed (association with multi-biologic failure with BMI, smoking, psoriasis severity) that did not reach statistical significance but that trended in the expected direction. The study was also conducted from 2006 to 2020, which includes a broad time range when fewer biologic agents were available, specifically, the IL-17 and IL-23 inhibitors. Therefore, data is limited on these agents which have reported higher efficacy than TNF-alpha and IL-12/23 agents in phase 3 studies.

Future Directions

While biologic agents have transformed the treatment landscape for psoriasis, real-world data highlights that certain patients are not responding to biologic agents or are experiencing a more rapid rate of efficacy loss. Further studies are needed to identify clinical and demographic factors associated with using or failing multiple biologic agents so clinicians and researchers can better characterize the phenotype of these patients and identify which therapies are best for them. The National Psoriasis Foundation (NPF) is launching a study to better characterize these patients, developing a novel crowd-sourced cloud database to track patients who fail multiple biologic agents on a nationwide scale. This database will allow clinicians to contribute cases of psoriasis patients who have failed multiple biologics or patients who have been successfully treated with a single agent. Information on patient demographics and clinical factors will also be collected. With a larger sample, we hope to strengthen the findings that have emerged from this study. Eventually, these forms of data collection might also be useful for obtaining information on patients with rare forms of psoriasis, including erythrodermic and generalized pustular psoriasis.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Elizabeth Wallace serves as a research investigator for Argenx, Pfizer, and Target RWE. Jose Scher has received research funding from UCB, Janssen, Abbvie, Pfizer, Novartis, Sanofi, and BMS. Tina Bhutani has received research funding from Abbvie, Celgene, Galderma, Janssen, Pfizer, Regeneron, and Sun. She has served as an advisor for Abbvie, Boehringer-Ingelheim, Bristol Myers Squibb, Pfizer, Leo, Lilly, and Novartis. April W. Armstrong serves as a research investigator and/or scientific advisor to AbbVie, BMS, Incyte, Leo, UCB, Janssen, Lilly, Novartis, Ortho Dermatologics, Sun, Dermavant, Dermira, Sanofi, Regeneron, Pfizer, and Modmed. George Gondo is an employee of the National Psoriasis Foundation. Stacie Bell is a former employee of the National Psoriasis Foundation. Wilson Liao has received research grant funding from Abbvie, Amgen, Janssen, Leo, Novartis, Pfizer, Regeneron, and TRex Bio.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

This study was IRB-approved at UCSF (#10-02830) and all subjects provided written informed consent.

ORCID iDs

Edward Hadeler https://orcid.org/0000-0002-3005-6529
Samuel Yeroushalmi https://orcid.org/0000-0002-8327-3279
George Gondo https://orcid.org/0000-0002-6468-0397
Stacie Bell https://orcid.org/0000-0002-9987-567X
Wilson Liao https://orcid.org/0000-0001-7883-6439

References

1. Levin EC, Gupta R, Brown G, Malakouti M, Koo J. Biologic fatigue in psoriasis. *J Dermatol Treat*. 2014;25(1):78-82. doi:10.3109/09546634.2013.826341.
2. Hsu L, Snodgrass BT, Armstrong AW. Antidrug antibodies in psoriasis: A systematic review. *Br J Dermatol*. 2014;170(2):261-273. doi:10.1111/bjd.12654.
3. Torres T, Puig L, Vender R, et al. Drug Survival of IL-12/23, IL-17 and IL-23 inhibitors for psoriasis treatment: A retrospective multi-country, multicentric cohort study. *Am J Clin Dermatol*. 2021;22(4):567-579. doi:10.1007/s40257-021-00598-4.
4. Marinas JE, Kim WB, Shahbaz A, Qiang JK, Greaves S, Yeung J. Survival rates of biological therapies for psoriasis treatment in real-world clinical practice: A Canadian multicentre retrospective study. *Australas J Dermatol*. 2018;59(1):e11-e14. doi:10.1111/ajd.12548.
5. No DJ, Inkeles MS, Amin M, Wu JJ. Drug survival of biologic treatments in psoriasis: A systematic review. *J Dermatol Treat*. 2018;29(5):460-466. doi:10.1080/09546634.2017.1398393.
6. Shalom G, Cohen AD, Ziv M, et al. Biologic drug survival in Israeli psoriasis patients. *J Am Acad Dermatol*. 2017;76(4):662-669. doi:10.1016/j.jaad.2016.10.033.
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. Noiles K, Vender R. Biologic survival. *J Drugs Dermatol*. 2009;8(4):329-333.
9. Doshi JA, Takeshita J, Pinto L, et al. Biologic therapy adherence, discontinuation, switching, and restarting among patients with psoriasis in the US Medicare population. *J Am Acad Dermatol*. 2016;74(6):1057-1065.e4. doi:10.1016/j.jaad.2016.01.048.
10. Chan SA, Hussain F, Lawson LG, Ormerod AD. Factors affecting adherence to treatment of psoriasis: Comparing biologic

therapy to other modalities. *J Dermatol Treat*. 2013;24(1): 64-69. doi:10.3109/09546634.2011.607425.

11. The BIOREP Study Group, Kojanova M, Cetkovska P, et al. Real-world evidence from more than 1000 patients treated with adalimumab for moderate-to-severe Psoriasis in the Czech Republic. *Dermatol Ther*. 2021;11(2):543-553. doi:10.1007/s13555-021-00499-8.
12. Iznardo H, Vilarrasa E, López-Ferrer A, Puig L. Real-world drug survival of guselkumab, ixekizumab and secukinumab for psoriasis. *Br J Dermatol*. 2021;185(3):660-662. doi:10.1111/bjd.20416.
13. Mourad AI, Gniadecki R. Biologic drug survival in Psoriasis: A systematic review & comparative meta-analysis. *Front Med*. 2021;7:625755. doi:10.3389/fmed.2020.625755.
14. Chatzimichail G, Günther J, Ständer S, Thaçi D. Drug survival of secukinumab, ustekinumab, and certolizumab pegol in psoriasis: A 2-year, monocentric, retrospective study. *J Dermatol Treat*. 2021;33:1-5. doi:10.1080/09546634.2020.1854428.
15. Liao W, Singh R, Lee K, et al. Erythrodermic psoriasis: Pathophysiology and current treatment perspectives. *Persönlichkeitsstörungen Theor Ther (PTT)*. 2016;6:93-104. doi:10.2147/PTT.S101232.
16. Hadeler E, Mosca M, Hong J, Brownstone N, Bhutani T, Liao W. Nail Psoriasis: A review of effective therapies and recommendations for management. *Dermatol Ther* 2021;11(3): 799-831. doi:10.1007/s13555-021-00523-x.
17. Hong JJ, Mosca ML, Hadeler EK, Brownstone ND, Bhutani T, Liao WJ. Genital and Inverse/Intertriginous Psoriasis: An updated review of therapies and recommendations for practical management. *Dermatol Ther* 2021;11(3):833-844. doi:10.1007/s13555-021-00536-6.
18. Mosca M, Hong J, Hadeler E, Brownstone N, Bhutani T, Liao W. Scalp Psoriasis: A literature review of effective therapies and updated recommendations for practical management. *Dermatol Ther* 2021;11(3):769-797. doi:10.1007/s13555-021-00521-z.
19. Mitchell BL, Saklatvala JR, Dand N, et al. Genome-wide association meta-analysis identifies 29 new acne susceptibility loci. *Nat Commun*. 2022;13(1):702. doi:10.1038/s41467-022-28252-5.
20. De Pessemier B, Grine L, Debaere M, Maes A, Paetzold B, Callewaert C. Gut-skin axis: Current knowledge of the interrelationship between microbial dysbiosis and skin conditions. *Microorganisms*. 2021;9(2):353. doi:10.3390/microorganisms9020353.
21. Myers B, Brownstone N, Reddy V, et al. The gut microbiome in psoriasis and psoriatic arthritis. *Best Pract Res Clin Rheumatol*. 2019;33(6):101494. doi:10.1016/j.berh.2020.101494.
22. Navarro-López V, Núñez-Delegido E, Ruzafa-Costas B, Sánchez-Pellicer P, Agüera-Santos J, Navarro-Moratalla L. Probiotics in the Therapeutic Arsenal of Dermatologists. *Microorganisms*. 2021;9(7):1513. doi:10.3390/microorganisms9071513.
23. Lee YB, Byun EJ, Kim HS. Potential Role of the Microbiome in Acne: A comprehensive review. *J Clin Med*. 2019;8(7):E987. doi:10.3390/jcm8070987.
24. Yan H, Su R, Xue H, Gao C, Li X, Wang C. Pharmacomicrobiology of methotrexate in rheumatoid arthritis: gut microbiome as predictor of therapeutic response. *Front Immunol*. 2021;12:789334. doi:10.3389/fimmu.2021.789334.
25. Dand N, Duckworth M, Baudry D, et al. HLA-C*06:02 genotype is a predictive biomarker of biologic treatment response in psoriasis. *J Allergy Clin Immunol*. 2019;143(6):2120-2130. doi:10.1016/j.jaci.2018.11.038.
26. van Vugt LJ, van den Reek JMPA, Hannink G, Coenen MJH, de Jong EMGJ. Association of HLA-C*06:02 status with differential response to ustekinumab in patients with psoriasis: A systematic review and meta-analysis. *JAMA Dermatol*. 2019; 155(6):708-715. doi:10.1001/jamadermatol.2019.0098.
27. Enamandram M, Kimball AB. Psoriasis epidemiology: the interplay of genes and the environment. *J Invest Dermatol*. 2013; 133(2):287-289. doi:10.1038/jid.2012.434.
28. Davison SC, Allen MH, Mallon E, Barker JNWN. Contrasting patterns of streptococcal superantigen-induced T-cell proliferation in guttate vs. chronic plaque psoriasis. *Br J Dermatol*. 2001;145(2):245-251. doi:10.1046/j.1365-2133.2001.04341.x.
29. McFadden JP, Baker BS, Powles AV, Fry L. Psoriasis and streptococci: the natural selection of psoriasis revisited. *Br J Dermatol*. 2009;160(5):929-937. doi:10.1111/j.1365-2133.2009.09102.x.
30. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM, Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol*. 2013;133(2):377-385. doi:10.1038/jid.2012.339.