Effectiveness and persistence of acitretin, ciclosporin, fumaric acid esters and methotrexate for patients with moderate-to-severe psoriasis: a cohort study from BADBIR

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Abstract

Background: Real-world data evaluating effectiveness and persistence of systemic therapies for patients with psoriasis are limited.

Objectives: To determine the effectiveness and persistence of acitretin, ciclosporin, fumaric acid esters (FAEs) and methotrexate in patients with moderate-to-severe psoriasis.

Methods: Data from The British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR), a prospective, multi-centre pharmacovigilance register of patients with moderate-to-severe psoriasis receiving biologic and/or conventional systemic therapies, were analysed. Eligible patients were ≥16 years of age receiving a first course of acitretin, ciclosporin, FAEs or methotrexate between 2007 and 2021 with ≥6 months' follow-up. Effectiveness was defined as achieving absolute Psoriasis Area and Severity Index (aPASI) ≤2 reported ≥4 weeks after treatment start date until stop date. To identify baseline clinical variables associated with treatment effectiveness, we used multivariable logistic regression models estimating the adjusted odds ratio (aOR) of achieving aPASI ≤2. To describe drug persistence associated with ineffectiveness, occurrence of adverse events or other reasons of discontinuation, survival estimates with 95% confidence interval (CI) were obtained using a flexible parametric model. Results were obtained using multiple imputed data.

Results: In total, 5430 patients were included in the analysis: 1023 (19%) on acitretin, 1401 (26%) ciclosporin, 347 (6%) FAEs and 2659 (49%) methotrexate at registration. The proportion of patients who achieved aPASI≤2 was lower with acitretin 118 (21%) compared with those on ciclosporin 233 (34%), FAEs 43 (30%) and methotrexate 372 (32%). Factors associated with ineffectiveness included prior experience to previous non-biologic systemic therapies (acitretin) [(aOR, (95% CI) 0.64 (0.42, 0.96)], male sex (methotrexate) 0.58 (0.46, 0.74), co-morbidities 0.70 (0.51, 0.97) and alcohol consumption (≤14 units per week) (ciclosporin) 0.70 (0.50, 0.98). Persistence associated with all reasons of discontinuation showed better survival for methotrexate compared with acitretin, ciclosporin and FAEs cohorts at 12 months [(Survival estimate (95% CI), 46.1 (44.0, 48.3), 31.9 (29.4, 34.7), 30.0 (27.5, 32.4) and 35.0 (29.9, 40.9)], respectively.

Conclusions: The real-world effectiveness and persistence of acitretin, ciclosporin, FAEs and methotrexate were generally low. Previous non-biologic systemic therapies, male sex, comorbidities and alcohol consumption were risk factors associated with treatment ineffectiveness.

Introduction

Plaque psoriasis is a chronic, inflammatory skin disease affecting at least 60 million people worldwide and associated with significant comorbidities and poor quality of life. [1] The European Dermatology Forum (EDF) and the National Institute for Health and Care Excellence (NICE) recommend the use of standard non-biologic systemic therapy for the treatment of moderate-to-severe psoriasis that cannot be controlled with topical treatments or phototherapy. The same guidelines recommend that age, disease phenotype, previous treatment history, disease severity, the presence of psoriatic arthritis, conception plan and comorbidities should be considered when prescribing standard systemic therapy. [2,3]

Randomised controlled trials (RCT) are considered the gold standard to assess the effectiveness of therapies. However, trials related to acitretin, ciclosporin, fumaric acid esters (FAEs) and methotrexate for the treatment of psoriasis have been restricted to small sample sizes, short-term follow-up, strict inclusion criteria and controlled environments, and therefore do not necessarily reflect real-world clinical practice. [4-6] Observational studies better represent routine clinical practice, usually with large sample size for group comparison and longer follow-up and are cost-effective to conduct as data are already collected. [5]

A systematic review conducted by our group showed the lack of large observational studies evaluating the safety and effectiveness of non-biologic systemic therapies in patients with psoriasis. [7] The British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR), is a prospective, multicentre, pharmacovigilance register designed to assess the long-term safety and effectiveness of systemic therapy in patients with moderate-to-severe psoriasis. BADBIR was established in 2007 and, currently includes more than 20,000 patient registrations recruited from 164 dermatological centres across the UK and the Republic of Ireland (RoI). The aim of this study was to determine the effectiveness and persistence of acitretin, ciclosporin, FAEs or methotrexate in patients with moderate-to-severe psoriasis registered to BADBIR and to evaluate potential risk factors associated with treatment ineffectiveness.

Materials and methods

Data source

Detailed information on BADBIR design and follow-up visits has been published previously. [8] BADBIR received approval from the North West Research Ethics Committee in March 2007.

Baseline and follow-up assessments

Patient-level data concerning demographics, comorbidities, disease factors and, treatment details were extracted from BADBIR. Baseline Psoriasis Area and Severity Index (PASI) and baseline Dermatology Life Quality Index (DLQI) were reported within 6 months of drug start date (−183 to 0 days). Drug discontinuation was defined as any gap in treatment for more than 90 days. Treatment courses continued throughout the study period until December 2021, or those lost to follow-up were considered censored. Further details are shown in the supporting information.

Study population

Eligible patients were registered to BADBIR between September 2007 and December 2021, aged ≥16 years, with moderate-to-severe psoriasis defined as PASI of ≥10 and DLQI >10, [2, 10] receiving either acitretin, ciclosporin, FAEs or methotrexate as first treatment course, monotherapy and had completed a minimum of 6 months' follow-up. The final analytical cohort and number of excluded records are presented in Figure 1.

Study Design

A pre-maintenance period was introduced by excluding any PASI records within 30 days of treatment initiation. [6] This is to address the dose-titration (increase/decrease) and the effect of previous psoriasis treatment. A maintenance period was defined as between the pre-maintenance period until treatment discontinuation. PASI records within the maintenance period were included in measuring effectiveness. In case of multiple PASI records within the maintenance period, a minimum value was selected. A schematic diagram showing these periods is presented in Figure S1 (supporting information).

Primary outcome(s)

1. Achieving absolute PASI (aPASI) ≤2, corresponds to a reduction of 90% in baseline PASI (PASI 90), [11] at any time during treatment from 4 weeks after initiation until treatment stop date (maintenance period). Unlike relative PASI, aPASI has the advantage of being independent of baseline PASI, which is not always available in routine clinical practice, and reflects the disease severity at the time of analysis. [12]
2. Drug persistence, defined as the duration between drug initiation to discontinuation or censoring at the latest follow-up. Reasons for discontinuation were ineffectiveness, occurrence of adverse events or other reasons (including contraindication, financial consideration, patient choice, patient non-compliance, remission and clinical trial enrolment).

Secondary outcome

Achieving aPASI ≤4, corresponds to PASI 75, [11] at any time during treatment from 4 weeks after initiation until treatment stop date.

Exposure

Treatment choice defined as receiving acitretin, ciclosporin, FAEs or methotrexate as a first course of treatment at registration.

Statistical Analysis

Baseline characteristics

Descriptive analysis was performed with summary statistics of percentages to describe categorical variables and means with standard deviations (SD) or median with inter-quartile ranges (25%, 75% IQR) for continuous variables.

Risk factors associated with treatment ineffectiveness

To identify baseline clinical variables associated with treatment effectiveness, we used a multivariable logistic regression model estimating the adjusted odds ratio (aOR) of achieving aPASI ≤2 and aPASI ≤4 (coded as 1). The overall model was adjusted for a number of factors measured at baseline including: i) binary variables (yes/no): previous standard non-biologic systemic therapies, sex, smoking, the presence of comorbidities (see supporting information), and psoriatic arthritis; ii) categorical variables: alcohol consumption (no alcohol, alcohol consumption ≤14 units per week and alcohol consumption >14 units per week); iii) continuous variables: age at treatment initiation, disease duration calculated from treatment initiation date, body mass index (BMI), PASI and DLQI; iv) interactions to obtain OR at each level of treatment choice were added. Covariates were selected on the basis of NICE guideline, [3] prior knowledge and model fit diagnosis. Goodness of fit for the final model was tested using Hosmer-Lemeshow test and the Bayesian Information Criterion (BIC) with the lowest BIC selected as the final model. As a sensitivity analysis, stratified logistic models were fitted separately within each systemic cohort adjusted for the same factors in the overall model using aPASI≤2 (Table S1) and aPASI≤4 (Table S2) (supporting information).

Persistence

To describe overall persistence associated with ineffectiveness, occurrence of adverse events or other reasons, survival estimates with 95% confidence interval (CI) were obtained using a flexible parametric model. [13] To compare persistence between treatments, an overall survival model included treatment choice and adjusted for the same covariates mentioned above was fitted. Methotrexate was chosen as the reference, since it is the first systemic choice after topical therapy [3] and with the largest sample size. Estimating standardised survival curve to a common distribution of confounders allows correction for the different distribution of baseline covariates between treatment cohorts. [14] This is particularly important when comparing between groups to ensure that the treatment cohorts are similar in their baseline characteristics therefore the comparison is less biased. The proportional excess hazards assumption was assessed by including treatment choice as a time-dependent effects and tested using the likelihood ratio test by comparing two models with and without time dependent effects. To account for missing data, we used multiple imputation (see supporting information). All tests were two-tailed, the level of statistical significance pre-specified at 5% ($p < 0.05$) and estimates derived with 95% CIs. All statistical analyses were performed using Stata version 17.0 (StataCorp).

Results

Baseline characteristics

A total of 5430 psoriasis patients were included in the analysis (Figure 1), of those 1023 (19%) were on acitretin, 1401 (26%) ciclosporin, 347 (6%) FAEs and 2659 (49%) methotrexate at registration. Patients on ciclosporin were younger [median age years (IQR), 37 (29, 48)] compared with those on acitretin, FAEs and methotrexate [median age years (IQR), 49 (39, 60), 44 (34, 53) and 44 (33, 54)], respectively. A minority of patients on acitretin were women 268 (26%) compared with those on ciclosporin 688 (49%), FAEs 145 (42%) and methotrexate 1279 (48%). Patients on FAEs were less likely to be systemic naïve 70 (20%) compared with those on acitretin 482 (47%), ciclosporin 593 (42%) and methotrexate 1212 (46%) (Table 1).

Effectiveness

1. *Achieving absolute PASI≤2 and PASI≤4*

Median time to achieve aPASI≤2 was shorter on ciclosporin [Median months (IQR) 5.5 (3.1, 8.9)] compared with methotrexate 9.2 months (6.1, 15.4), acitretin 10.4 months (5.7, 16.5) and FAEs 11.9 months (5.8, 24.4). Likewise, median time to achieve aPASI≤4 was shorter on ciclosporin [Median months (IQR) 5.5 (3.1, 8.2)] compared with methotrexate 8.1 months (5.3, 13.3), acitretin 9.1 (4.8, 15.3) and FAEs 9.0 months (5.5, 15.7) (Table 2). Median PASI, during the exposure period, was slightly lower on ciclosporin and methotrexate compared with FAEs and acitretin [Median (IQR) 3.8 (1.2, 10.0) and 3.9

(1.5, 9.2) vs. 4.9 (1.6, 11.5) and 5.9 (2.4, 11.0), respectively]. The proportion of patients who achieved aPASI≤2 was lower on acitretin 118 (21%) compared with those on ciclosporin 233 (34%), FAEs 43 (30%) and methotrexate 372 (32%). Higher proportions of patients on all drugs achieved aPASI≤4 compared with aPASI≤2 [total (%) acitretin 224 (40), ciclosporin 354 (51), FAEs 69 (47) and methotrexate 602 (52)] (Table 2).

2. Risk factors associated with treatment ineffectiveness

Results from the logistic model showed that prior treatment with non-biologic systemic therapies does not influence outcomes to methotrexate, ciclosporin or FAEs. However, patients on acitretin who had received previous non-biologic systemic therapies were less likely to achieve effectiveness compared with their acitretin naïve counterparts [(aOR, (95% CI) 0.64 (0.42, 0.96)] (Table 3). Male sex was associated with reduced effectiveness in patients on methotrexate 0.58 (0.46, 0.74) but not with other therapies. However, men on methotrexate presented with a significantly higher median PASI measured during treatment exposure than women [Median (IQR) 5.0 (2.0, 10.8) vs. 3.0 (1.0, 7.4)]. The presence of comorbidities and consumption of less than 14 units of alcohol per week were significantly associated with reduced effectiveness in patients on ciclosporin [0.70 (0.51, 0.97) and 0.70 (0.50, 0.98), respectively]. Consumption of >14 units of alcohol per week was not associated with ineffectiveness in any of the four therapies (Table 3). Patients on methotrexate with a high BMI 0.98 (0.96, 1.00), longer disease duration on methotrexate [0.98 (0.97, 0.99)] and in those on acitretin0.99 (0.97, 1.00), higher baseline PASI on acitretin, ciclosporin and methotrexate [0.96 (0.92, 1.00), 0.97 (0.94, 0.99) and 0.97 (0.95, 0.99), respectively] were significantly associated with not achieving aPASI≤2. However, these effect sizes were small; for example, aOR of baseline PASI could be interpreted as each additional increase of one unit in baseline PASI is associated with 4% and 3% decrease in the odds of achieving aPASI≤2 in patients on acitretin, ciclosporin and methotrexate. Age, however, was significantly associated with achieving aPASI≤2 in patients on acitretin 1.02 (1.00, 1.03), FAEs 1.03 (1.00, 1.06) and methotrexate 1.03 (1.02, 1.03). This means that each additional increase of one year in age is associated with 2% and 3% increase in the odds of achieving effectiveness in patients on acitretin, FAEs and methotrexate (Table 3).

3. Achieving absolute PASI≤4

Higher proportions of patients on all drugs achieved aPASI≤4 compared with aPASI≤2 [total (%) acitretin 224 (40), ciclosporin 354 (51), FAEs 69 (47) and methotrexate 602 (52)] (Table 2). Results from the logistic model of achieving aPASI≤4 were compatible with those obtained using aPASI≤2 (Table 4).

4. Sensitivity analysis

Results from the stratified logistic models were similar to the main logistic model in direction and magnitude (Tables S1 and S2, supporting information).

Persistence

Overall persistence showed a better survival for methotrexate compared with acitretin, ciclosporin and FAEs cohorts at 6 months [(Survival estimate (95% CI), 66.5 (64.7, 68.3), 54.4 (51.8, 57.1), 55.1 (52.8, 57.6) and 55.1 (50.0, 61.0)] and at 12 months [46.1 (44.0, 48.3), 31.9 (29.4, 34.7), 30.0 (27.5, 32.4) and 35.0 (29.9, 40.9), respectively] (Table 2) (Figure 2). When stratifying persistence into reasons of discontinuation, acitretin had a lower persistence compared with ciclosporin, FAEs and methotrexate due to ineffectiveness at 6 months [70.3 (67.3, 73.0), 82.9 (80.9, 85.0), 80.1 (75.3, 85.2) and 79.6 (78.0, 81.3)] and at 12 months [53.4 (50.2, 56.8), 67.6 (64.5, 70.7), 69.3 (63.0, 76.2) and 68.0 (65.9, 70.3), respectively] (Table 2) (Figure 3). However, methotrexate sustained a better persistence due to the occurrence of adverse events followed by acitretin, ciclosporin and FAEs at 6 months [87.5 (86.2, 88.9), 84.1 (81.9, 86.3), 79.8 (77.7, 82.0) and 72.8 (67.8, 78.2)] and 12 months [76.1 (74.0, 78.2), 72.1 (69.1, 75.3), 65.3 (62.3, 68.4) and 57.3 (51.1, 64.3), respectively] (Table 2) (Figure 4).

Discussion

This real-world study has shown that the effectiveness of acitretin, ciclosporin, FAEs and methotrexate prescribed for moderate-to-severe psoriasis patients is generally low. Methotrexate had the best overall persistence. However, when stratifying persistence by stopping reason, acitretin had the lowest persistence associated with ineffectiveness while methotrexate sustained a better persistence corresponding to the occurrence of adverse events. Furthermore, factors associated with reduced drug effectiveness included male sex (methotrexate), co-morbidities and alcohol consumption (ciclosporin) and prior experience to therapy (acitretin).

Effectiveness

We measured effectiveness at any time during treatment from 4 weeks after initiation until treatment discontinuation using either aPASI≤2 or aPASI≤4 corresponding to PASI90 and PASI75, respectively. [11] Direct comparison with previous studies is not necessarily appropriate due to different study designs, definitions of effectiveness and timing. For example, the proportion of patients achieving aPASI≤4 at any time since methotrexate initiation was higher than the proportion of patients achieving PASI75 at week 16 of methotrexate initiation (52% vs. 35.5%) in the CHAMPION trial comparing between methotrexate, adalimumab and placebo. [15] Nevertheless, our finding of 32% patients on methotrexate achieving

aPASI≤2 was consistent with this trial [15] and the 37% of patients achieving PASI75 at week 12 using the real-world data of the Swiss Dermatology Network for Targeted Therapies (SDNTT) registry. [4] Our finding of 21% of patients on acitretin achieving aPASI≤2 was consistent with an Italian cohort study in which 21.9% of patients on acitretin achieved PASI90. [16]

Risk factors associated with treatment ineffectiveness

We showed that response to methotrexate was sex related as men were less likely to achieve aPASI≤2 or aPASI≤4 compared with women. This finding is consistent with results from the national psoriasis registries of Germany (PsoBest) and SDNTT in which women showed a significantly better response to acitretin, ciclosporin, FAEs and methotrexate compared with men at months 3, 6 and 12 of treatment. [17] However, in our study sex difference in response to treatment was significant in the methotrexate cohort only, this could be explained by the relatively smaller numbers in the other cohorts. This sex-related response could be explained by higher drug adherence and lower body weight in women (which could result in higher dose per kilogram), or hormonal status. [17] A trend in sex differences was also seen in response to biologics including adalimumab, etanercept and ustekinumab in which women were less likely to achieve effectiveness (PASI 90) at 6 months following biologic initiation. [18] Previous experience to non-biologic systemic therapies, comorbidities and alcohol consumption of ≤14 units of alcohol per week were not associated with achieving aPASI≤2 or aPASI≤4 in patients on acitretin, and ciclosporin. However, alcohol consumption of >14 units per week was not associated with ineffectiveness in any of the four agents. Perhaps this could be explained by the smaller size within this category compared with those in the ≤14 units of alcohol per week. Age, BMI and baseline PASI were also associated with treatment ineffectiveness, yet the effect was very small.

Persistence

Our results revealed that methotrexate had a better persistence associated with all reasons compared with acitretin, ciclosporin and FAEs. This difference, however, attenuated when accounting for the presence of adverse events. Interestingly, acitretin had the lowest persistence due to ineffectiveness. We showed that our survival estimates at 1 year following acitretin, ciclosporin and methotrexate initiation were 32%, 30% and 46% due to all reasons, 53%, 68% and 68% due to ineffectiveness and 72%, 65% and 76% due to adverse of events, respectively. This is consistent with findings from BIOBADADERM, a Spanish biologics registry of moderate-to-severe psoriasis patients [19] of 1 year survival in response to ciclosporin and methotrexate due to all reasons 23% and 50%, ineffectiveness 68% and 80% and adverse of events 79% and 88%, respectively. Likewise, our results were consistent with survival estimates from a German

cohort of plaque psoriasis patients which showed similar overall survival rates at 1 year for psoriasis patients on acitretin and methotrexate 37% and 43% respectively but lower for ciclosporin 16% compared with our results. [20] However, our survival estimates of all reasons at 1 year were slightly higher compared with findings from a large French National Health Database of 73,168 patients with psoriasis for ciclosporin (20%) and methotrexate (42%) but much higher for acitretin 15%. [21]

Clinical implications

We showed that real-world effectiveness and persistence of acitretin, ciclosporin, FAEs and methotrexate are generally low, particularly when compared to the data from biologic therapies. [22, 23] Previous results from BADBIR reported high overall persistence for biologics ranging from 75%-88% at one year of follow-up.[23] With the widespread availability and reduced costs of biosimilars, the eligibility criteria for initiation of biologics in the UK might be updated to enable these effective therapies to be used as an alternative to conventional systemic drugs for psoriasis. This could lead to optimal outcomes in real-world clinical practice.

Strengths and Limitations

Missing PASI records (Tables S3) could be explained by the additional care given to patients on biologics, but not to those on non-biologic systemic therapies, who were more likely to be seen in specialist clinics where PASI measurements are more frequently requested. In addition the high cost of biologics, compared with non-biologic systemic therapies, may lead to more frequent PASI measurements as a proxy of disease severity, to justify continuation. Therefore, a multiple imputation by chained equations to correct for this persistent issue was conducted. Results of patients' characteristics at baseline stratified by complete and missing primary outcome were similar (Table S4). Our data do not include information on the route of administration of methotrexate (oral vs. subcutaneous); subsequently, outcomes data of all methotrexate-treated patients were pooled regardless of route of administration.

Conclusion

The effectiveness and persistence of acitretin, ciclosporin, FAEs and methotrexate were generally low. Previous non-biologic systemic therapies, male sex, comorbidities and alcohol consumption were risk factors associated with treatment ineffectiveness. Findings from this large real-world cohort provide important information to aid clinicians and their patients when managing psoriasis with non-biologic systemic therapies.

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Data availability: The data underlying this article cannot be shared publicly due to linkages to other data health records which requires additional permission.

Ethics statement: BADBIR received approval from the North West Research Ethics Committee in March 2007. All participants provided written informed consent in accordance with the Declaration of Helsinki.

What is already known about this topic

- Randomised clinical trials have shown relatively low efficacy for acitretin, ciclosporin, fumaric acid esters (FAEs) and methotrexate for psoriasis.

What does this study add

- Using a large scale real-world dataset, we confirmed previous findings of low effectiveness and persistence of acitretin, ciclosporin, FAEs and methotrexate.
- Methotrexate had better persistence compared with acitretin, ciclosporin, FAEs.
- Predictors of ineffectiveness were previous experience to standard non-biologic systemic therapies, male sex, comorbidities and alcohol consumption.

References

1. Parisi R, Iskandar IYK, Kontopantelis E, Augustin M, Griffiths CEM, Ashcroft DM. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. Bmj. 2020;369:m1590.
2. European Dermatology Forum. Guideline for the systemic treatment of psoriasis vulgaris. Last updated October 2021. Available at: https://www.edf.one/home/Guidelines/EuroGuiDerm-psoriasis-vulgaris.html.
3. National Institute for Health and Care Excellence. Psoriasis: assessment and management. Clinical guideline CG153. Published: 24 October 2012. Last updated: 01 September 2017. Available at: https://www.nice.org.uk/Guidance/CG153.
4. Maul JT, Djamei V, Kolios AGA, Meier B, Czernielewski J, Jungo P, et al. Efficacy and Survival of Systemic Psoriasis Treatments: An Analysis of the Swiss Registry SDNTT. Dermatology. 2016;232(6):640-7.
5. Sharma M, Nazareth I, Petersen I. Observational studies of treatment effectiveness: worthwhile or worthless? Clin Epidemiol. 2019;11:35-42.
6. Sbidian E, Chaimani A, Garcia-Doval I, Doney L, Dressler C, Hua C, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2022;5(5):Cd011535.
7. Mason KJ, Williams S, Yiu ZZN, McElhone K, Ashcroft DM, Kleyn CE, et al. Persistence and effectiveness of nonbiologic systemic therapies for moderate-to-severe psoriasis in adults: a systematic review. Br J Dermatol. 2019;181(2):256-64.
8. Burden AD, Warren RB, Kleyn CE, McElhone K, Smith CH, Reynolds NJ, et al. The British Association of Dermatologists' Biologic Interventions Register (BADBIR): design, methodology and objectives. Br J Dermatol. 2012;166(3):545-54.
9. Leung KM, Elashoff RM, Afifi AA. Censoring issues in survival analysis. Annu Rev Public Health. 1997;18:83-104.
10. Mrowietz U, de Jong EM, Kragballe K, Langley R, Nast A, Puig L, et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol. 2014;28(4):438-53.
11. Mahil SK, Wilson N, Dand N, Reynolds NJ, Griffiths CEM, Emsley R, et al. Psoriasis treat to target: defining outcomes in psoriasis using data from a real-world, population-based cohort study (the British Association of Dermatologists Biologics and Immunomodulators Register, BADBIR). Br J Dermatol. 2020;182(5):1158-66.

12. Puig L, Dossenbach M, Berggren L, Ljungberg A, Zachariae C. Absolute and Relative Psoriasis Area and Severity Indices (PASI) for Comparison of the Efficacy of Ixekizumab to Etanercept and Placebo in Patients with Moderate-to-severe Plaque Psoriasis: An Integrated Analysis of UNCOVER-2 and UNCOVER-3 Outcomes. Acta Derm Venereol. 2019;99(11):971-7.
13. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002;21(15):2175-97.
14. Lambert P. Standardized survival functions 2017 [Available from: https://pclambert.net/software/stpm2_standsurv/standardized_survival/].
15. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008;158(3):558-66.
16. Chiricozzi A, Panduri S, Dini V, Tonini A, Gualtieri B, Romanelli M. Optimizing acitretin use in patients with plaque psoriasis. Dermatol Ther. 2017;30(2).
17. Maul JT, Augustin M, Sorbe C, Conrad C, Anzengruber F, Mrowietz U, et al. Association of sex and systemic therapy treatment outcomes in psoriasis: a two-country, multicentre, prospective, noninterventional registry study. Br J Dermatol. 2021;185(6):1160-8.
18. Warren RB, Marsden A, Tomenson B, Mason KJ, Soliman MM, Burden AD, et al. Identifying demographic, social and clinical predictors of biologic therapy effectiveness in psoriasis: a multicentre longitudinal cohort study. Br J Dermatol. 2019;180(5):1069-76.
19. Dávila-Seijo P, Dauden E, Carretero G, Ferrandiz C, Vanaclocha F, Gómez-García FJ, et al. Survival of classic and biological systemic drugs in psoriasis: results of the BIOBADADERM registry and critical analysis. J Eur Acad Dermatol Venereol. 2016;30(11):1942-50.
20. Arnold T, Schaarschmidt ML, Herr R, Fischer JE, Goerdt S, Peitsch WK. Drug survival rates and reasons for drug discontinuation in psoriasis. J Dtsch Dermatol Ges. 2016;14(11):1089-99.
21. Bergqvist C, Mezzarobba M, Weill A, Sbidian E. Persistence of treatment with conventional systemic agents for patients with psoriasis: a real-world analysis of 73 168 new users from the French National Health Insurance database. Br J Dermatol. 2020;182(6):1483-4.
22. Yiu ZZN, Mason KJ, Hampton PJ, Reynolds NJ, Smith CH, Lunt M, et al. Drug survival of adalimumab, ustekinumab and secukinumab in patients with psoriasis: a prospective cohort study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). Br J Dermatol. 2020;183(2):294-302.

23. Yiu ZZN, Becher G, Kirby B, Laws P, Reynolds NJ, Smith CH, et al. Drug Survival Associated With Effectiveness and Safety of Treatment With Guselkumab, Ixekizumab, Secukinumab, Ustekinumab, and Adalimumab in Patients With Psoriasis. JAMA Dermatol. 2022.

Figure Legends

Figure 1 STROBE diagram of exclusion of cases from BADBIR to derive the analytical cohort.

Figure 2 Adjusted standardised survival curves with 95% confidence intervals (CI) for discontinuation associated with all reasons.

Figure 3 Adjusted standardised survival curves with 95% confidence intervals (CI for discontinuation associated with ineffectiveness.

Figure 4 Adjusted standardised survival curves with 95% confidence intervals (CI) for discontinuation associated with the occurrence of adverse events.

1 Table 1 Patients' characteristics at baseline, stratified by non-biologic systemic therapies

	Acitretin	Ciclosporin	FAEs	Methotrexate
Total, n (%)	1023 (19)	1401 (26)	347 (6)	2659 (49)
Median age, years (IQR)	49 (39, 60)	37 (29, 48)	44 (34, 53)	44 (33, 54)
Female (n, %)	268 (26)	688 (49)	145 (42)	1279 (48)
Follow-up time, Median years (IQR)	2 (1, 4)	1 (1, 3)	2 (1, 4)	2 (1, 4)
Disease duration, Median years (IQR)	16 (8, 27)	15 (7, 23)	19 (11, 28)	16 (8, 27)
BMI, Median (IQR)	29 (26, 34)	29 (25, 33)	30 (26, 34)	29 (25, 34)
Baseline PASI, Median (IQR)	14 (11, 18)	15 (11, 20)	12 (10, 16)	14 (11, 18)
Baseline DLQI, Median (IQR)	15 (11, 20)	16 (12, 22)	14 (10, 20)	16 (12, 21)
Comorbidities, n (%)	606 (59)	637 (45)	220 (63)	1521 (57)
Ever smoked, n (%)	652 (69)	866 (66)	196 (62)	1644 (66)
Alcohol consumption ≤14 units per week, n (%)	412 (41)	653 (47)	149 (43)	1145 (43.3)
Alcohol consumption >14 units per week, n (%)	264 (26)	307 (22)	98 (28)	404 (15)
Psoriatic arthritis, n (%)	81 (8)	121 (9)	31 (9)	246 (9)
Treatment history - Systemic naïve, n (%)	482 (47)	593 (42)	70 (20)	1212 (46)
Patients who switch to biologic, n (%)	131 (13)	334 (24)	86 (25)	450 (17)

Abbreviation: IQR: Inter-quartile range; BMI: Body Mass Index; PASI: the Psoriasis Area and Severity Index; DLQI: Dermatology life quality index.

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1 Table 2 Results of effectiveness and persistence

		Acitretin	Ciclosporin	FAEs	Methotrexate
Effectiveness					
	Available PASI records, n (%)	563 (55)	689 (49)	148 (43)	1166 (44)
	aPASI≤2, n (%)	118 (21)	233 (34)	43 (29)	372 (32)
	Time to PASI≤2, median months (IQR)	10.4 (5.7, 16.5)	5.5 (3.1, 8.9)	11.9 (5.8, 24.4)	9.2 (6.1, 15.4)
	aPASI≤4, n (%)	224 (40)	354 (51)	69 (47)	602 (52)
	Time to PASI≤4, median months (IQR)	9.1 (4.8, 15.3)	5.5 (3.1, 8.2)	9.0 (5.5, 15.7)	8.1 (5.3, 13.3)
	PASI, median (IQR)	5.9 (2.4, 11.0)	3.8 (1.2, 10.0)	4.9 (1.6, 11.5)	3.9 (1.5, 9.2)
Persistence					
	Time to discontinuation, median (IQR)	5.5 (2.7, 10.5)	5.2 (2.7, 8.9)	4.4 (1.8, 9.2)	5.7 (2.4, 12.0)
6 months	Overall survival	54.4 (51.8, 57.1)	55.1 (52.8, 57.6)	55.1 (50.0, 61.0)	66.5 (64.7, 68.3)
	Ineffectiveness	70.3 (67.3, 73.0)	82.9 (80.9, 85.0)	80.1 (75.3, 85.2)	79.6 (78.0, 81.3)
	Adverse events	84.1 (81.9, 86.3)	79.8 (77.7, 82.0)	72.8 (67.8, 78.2)	87.5 (86.2, 88.9)
12 months	Overall survival	31.9 (29.4, 34.7)	30.0 (27.5, 32.4)	35.0 (29.9, 40.9)	46.1 (44.0, 48.3)
	Ineffectiveness	53.4 (50.2, 56.8)	67.6 (64.5, 70.7)	69.3 (63.0, 76.2)	68.0 (65.9, 70.3)
	Adverse events	72.1 (69.1, 75.3)	65.3 (62.3, 68.4)	57.3 (51.1, 64.3)	76.1 (74.0, 78.2)

Abbreviation: IQR: Inter-quartile range; aPASI: absolute PASI.

1 Table 3 Overall adjusted odds ratio (aOR) with 95% confidence intervals (CI) using absolute PASI≤2

Variable	Acitretin	Ciclosporin	FAEs	Methotrexate
Experienced systemic	**0.64 (0.42, 0.96)**	0.99 (0.73, 1.34)	0.72 (0.31, 1.66)	1.02 (0.81, 1.30)
Age at treatment initiation	**1.02 (1.00, 1.03)**	1.01 (1.00, 1.02)	**1.03 (1.00, 1.06)**	**1.03 (1.02, 1.03)**
Male-sex	1.06 (0.66, 1.70)	1.06 (0.79, 1.43)	1.02 (0.51, 2.08)	**0.58 (0.46, 0.74)**
Psoriatic arthritis	0.88 (0.35, 2.13)	0.90 (0.50, 1.62)	1.34 (0.41, 4.40)	1.02 (0.68, 1.55)
Comorbidities	0.71 (0.46, 1.10)	**0.70 (0.51, 0.97)**	0.70 (0.32, 1.54)	0.87 (0.68, 1.12)
Ever smoked	1.03 (0.66, 1.60)	1.25 (0.90, 1.73)	0.88 (0.41, 1.92)	1.04 (0.81, 1.33)
Alcohol consumption ≤14 units per week	0.66 (0.42, 1.04)	**0.70 (0.50, 0.98)**	0.78 (0.36, 1.67)	1.06 (0.83, 1.35)
Alcohol consumption >14 units per week	0.61 (0.36, 1.04)	0.94 (0.63, 1.40)	0.47 (0.18, 1.24)	0.70 (0.48, 1.03)
BMI	0.99 (0.96, 1.03)	0.99 (0.97, 1.02)	1.00 (0.95, 1.05)	**0.98 (0.96, 1.00)**
Disease duration	**0.99 (0.97, 1.00)**	1.00 (0.99, 1.02)	1.01 (0.99, 1.04)	**0.98 (0.97, 0.99)**
Baseline PASI	**0.96 (0.92, 1.00)**	**0.97 (0.94, 0.99)**	1.00 (0.94, 1.06)	**0.97 (0.95, 0.99)**
Baseline DLQI	0.99 (0.96, 1.03)	1.00 (0.98, 1.02)	1.00 (0.94, 1.05)	0.99 (0.97, 1.01)

Abbreviation: BMI: Body Mass Index; PASI: The Psoriasis Area and Severity Index; DLQI: Dermatology life quality index; Bold odds ratio and CIs: significant p value (<0.05). Model adjusted for i) binary variables (yes/no): previous non-biologic systemic therapies (experienced systemic), sex, smoking, the presence of comorbidity including psoriatic arthritis; ii) categorical variables: alcohol consumption (no alcohol, alcohol consumption ≤14 units per week and alcohol consumption >14 units per week); iii) continuous variables: age at treatment initiation, disease duration calculated from treatment initiation date, body mass index (BMI), PASI and DLQI.

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1 Table 4 Overall adjusted odds ratio (aOR) with 95% confidence intervals (CI) using absolute PASI≤4

Variable	Acitretin	Ciclosporin	FAEs	Methotrexate
Experienced systemic	**0.70 (0.51, 0.95)**	0.80 (0.61, 1.04)	0.60 (0.30, 1.22)	1.14 (0.94, 1.40)
Age	**1.01 (1.00, 1.02)**	1.00 (0.99, 1.02)	**1.04 (1.02, 1.07)**	**1.01 (1.01, 1.02)**
Male-sex	0.97 (0.67, 1.40)	1.12 (0.87, 1.45)	1.31 (0.71, 2.41)	**0.66 (0.55, 0.80)**
Psoriatic arthritis	1.04 (0.55, 1.96)	0.85 (0.51, 1.41)	1.04 (0.35, 3.09)	0.89 (0.63, 1.25)
Comorbidities	0.73 (0.51, 1.03)	**0.70 (0.53, 0.92)**	0.62 (0.32, 1.19)	0.97 (0.79, 1.19)
Ever smoked	1.15 (0.81, 1.64)	1.26 (0.95, 1.66)	1.05 (0.58, 1.91)	1.02 (0.83, 1.24)
Alcohol consumption ≤14 units per week	0.85 (0.60, 1.21)	**0.71 (0.53, 0.95)**	0.88 (0.46, 1.71)	0.91 (0.75, 1.12)
Alcohol consumption >14 units per week	0.70 (0.46, 1.07)	0.88 (0.62, 1.24)	0.49 (0.22, 1.09)	0.90 (0.67, 1.19)
BMI	0.99 (0.96, 1.01)	0.99 (0.97, 1.01)	1.00 (0.96, 1.04)	**0.98 (0.97, 1.00)**
Disease duration	0.99 (0.98, 1.00)	1.01 (1.00, 1.02)	1.01 (0.99, 1.03)	**0.99 (0.98, 1.00)**
Baseline PASI	**0.95 (0.93, 0.98)**	**0.97 (0.95, 0.99)**	0.99 (0.92, 1.06)	**0.98 (0.96, 0.99)**
Baseline DLQI	0.99 (0.96, 1.02)	0.99 (0.97, 1.01)	0.98 (0.94, 1.02)	0.99 (0.98, 1.01)

Abbreviation: BMI: Body Mass Index; PASI: The Psoriasis Area and Severity Index; DLQI: Dermatology life quality index; Bold odds ratio and CIs: significant p value (<0.05). Model adjusted for i) binary variables (yes/no): previous non-biologic systemic therapies (experienced systemic), sex, smoking, the presence of comorbidity including psoriatic arthritis; ii) categorical variables: alcohol consumption (no alcohol, alcohol consumption ≤14 units per week and alcohol consumption >14 units per week); iii) continuous variables: age at treatment initiation, disease duration calculated from treatment initiation date, body mass index (BMI), PASI and DLQI

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1 Figure 1 STROBE diagram of exclusion of cases from BADBIR to derive the analytical cohort

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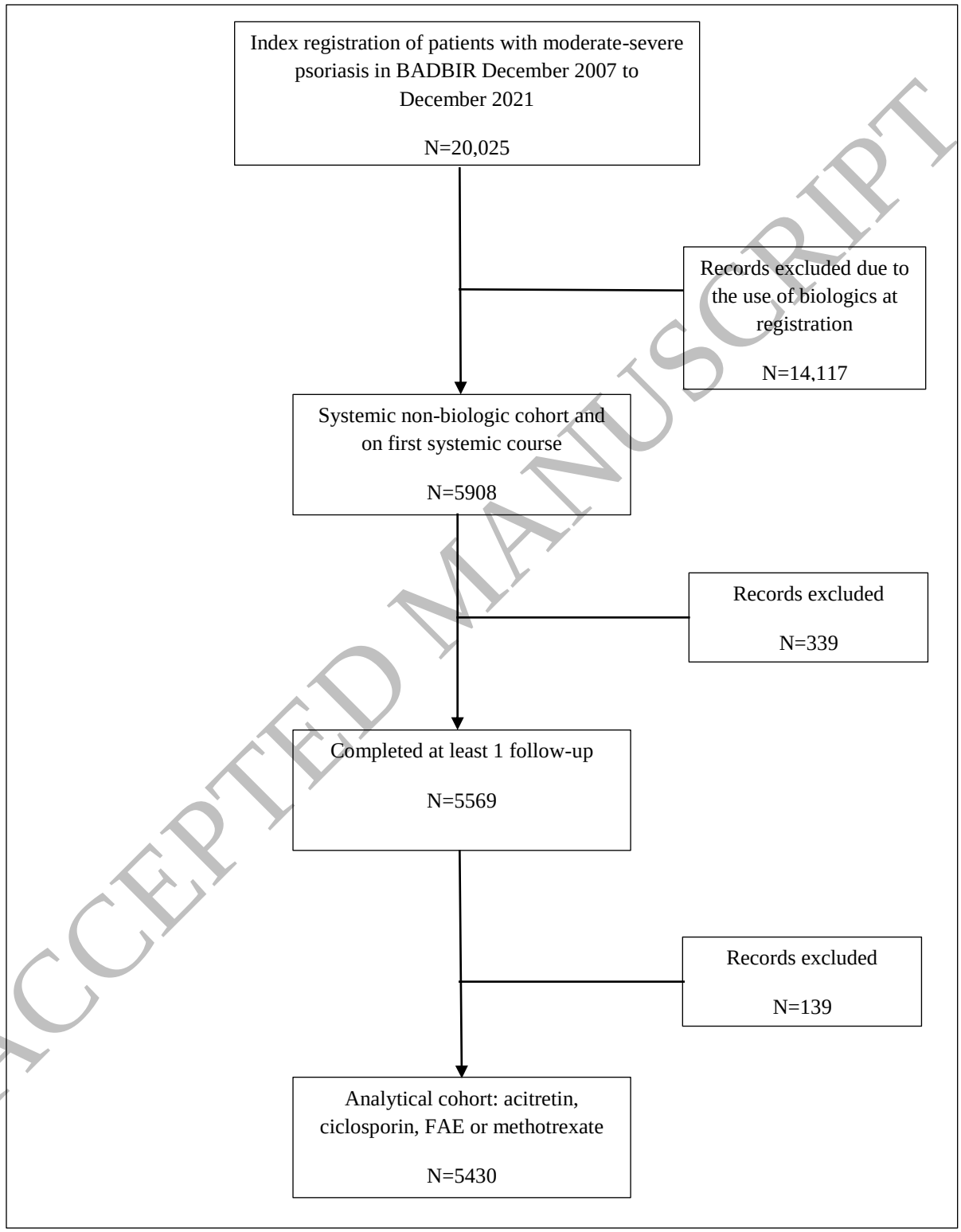

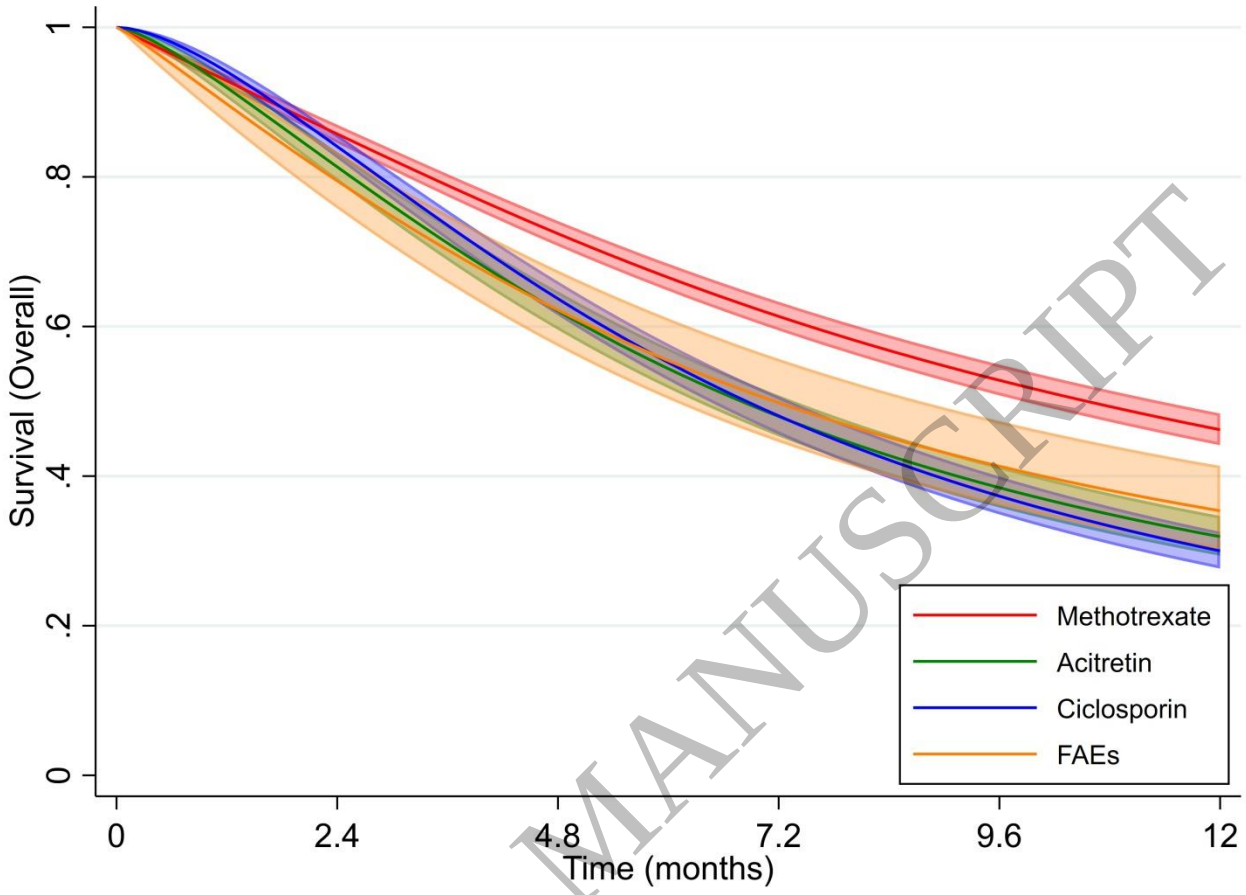

Figure 2
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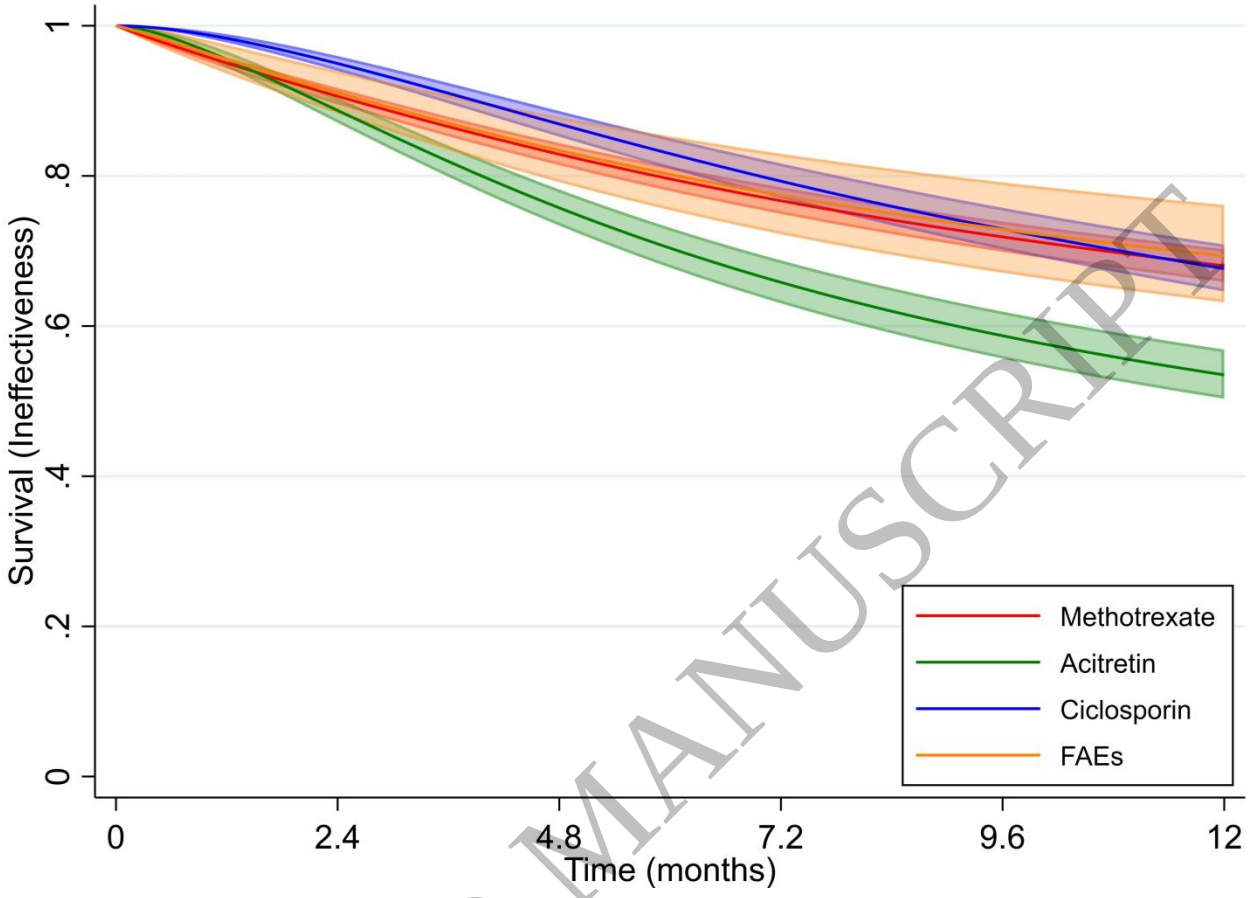

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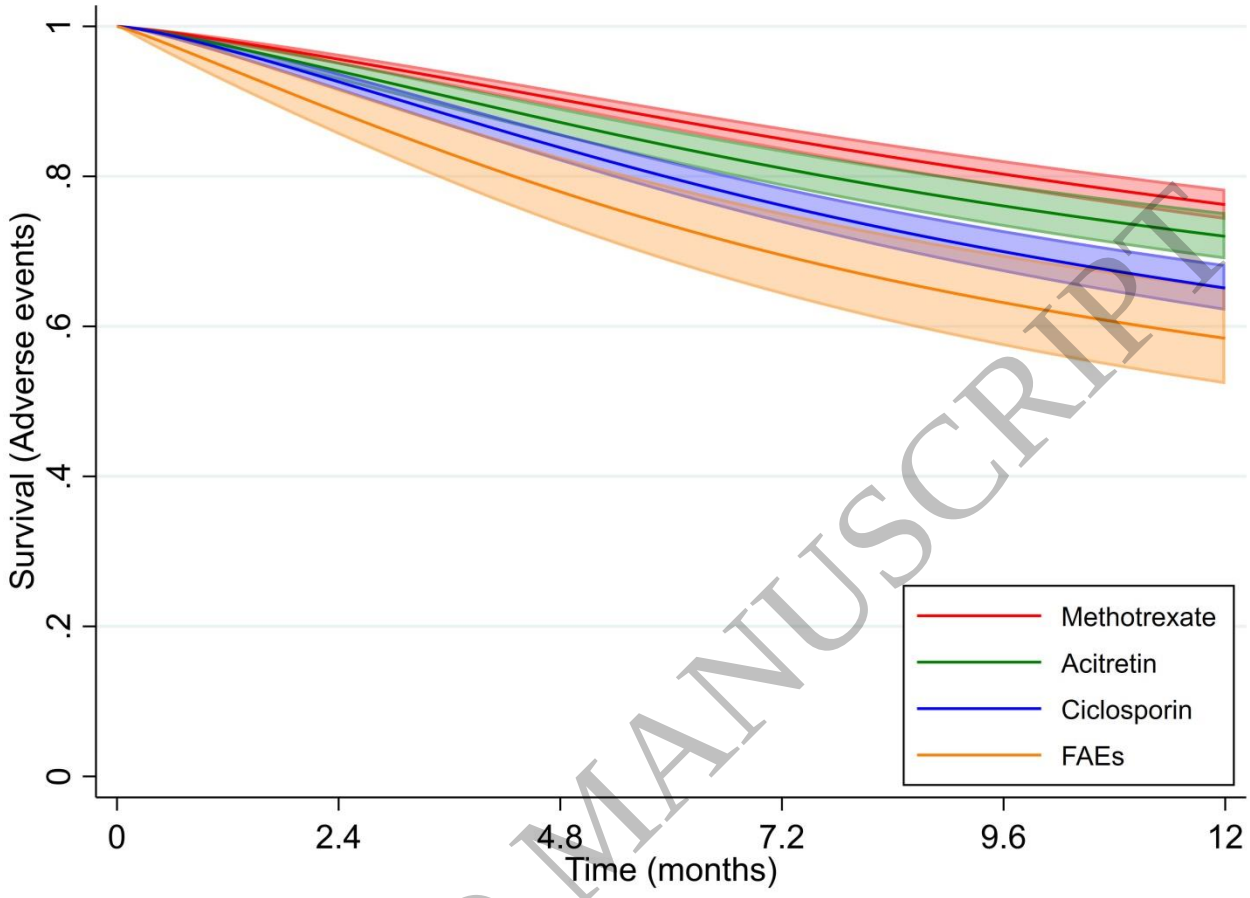

Figure 4
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