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Declarations: This manuscript contains original unpublished work and is not being submitted for publication elsewhere at the same time. All of the authors have made a substantial contribution to the study in accordance with international criteria and have revised and approved the final manuscript.

Data availability statement: The data that support the findings of this study are available from the BIOBADADERM study group, upon reasonable request.

Ethics: Observational study. Approved (BIOBADADERM: Hospital Universitario 12 de Octubre (216/07).

Key words: psoriasis, safety, adverse events, combined treatment, biologic therapy, prospective cohort.

Bulleted statements:

What's already known about this topic?

- The combination of a biologic agent and methotrexate (MTX) is frequently observed in patients with psoriasis in current clinical practice.
- There is little evidence on the safety of combining biologic drugs with MTX in psoriasis treatment, especially with the interleukin (IL) 17 and IL-23 inhibitors.

What does this study add?

- The combination of MTX with a tumor necrosis factor (TNF), IL-17 and IL-23 inhibitors in patients with moderate to severe psoriasis in real-life does not significantly increase the risk of adverse events, serious adverse events or infections compared to monotherapy with the same biologic drugs.

ABSTRACT

Background: Safety is an important consideration in decisions on treatment for patients with moderate to severe psoriasis and its study is the main purpose of the BIOBADADERM Registry. The combination of a biologic agent and a conventional systemic drug— generally methotrexate (MTX)—is a common treatment in clinical practice. However, there is a paucity of evidence from real-world practice on the safety of such combination regimens in psoriasis.

Objectives: The primary objective of this study was to ascertain whether the use of regimens combining biologic drugs with MTX in the management of moderate to severe psoriasis increases the risk of adverse events (AEs) or serious AEs (SAEs). We compared monotherapy with tumour necrosis factor (TNF), interleukin-17 and interleukin-23 inhibitors with the use of the same drugs in combination with MTX.

Methods: Using data from the BIOBADADERM Registry, we compared biologic monotherapies with MTX combined therapies. We estimated crude and adjusted incidence rate ratios using a random effects Poisson regression with 95% confidence intervals for all AEs, SAEs, infections and serious infections, and several organ class systems.

Results: We analysed data from 2,829 patients and 5,441 treatment cycles, a total of 12,853 patient-years. The combination of a biologic with MTX was not associated with statistically significant increases in overall risk of AEs or SAEs in any treatment group. No increase in the total number of infections or serious infections in patients receiving combined therapy was observed for any group. However, treatment with a TNF inhibitor plus MTX was associated with an increase in the incidence of gastrointestinal AEs.

Conclusions: The risk of AEs and SAEs was not significantly increased in patients with moderate to severe psoriasis receiving different classes of biologic drugs plus MTX compared to those on biologic monotherapy.

INTRODUCTION

Psoriasis is an inflammatory skin disease with multiple associated comorbidities[1,2], some of which may condition the choice of treatment[3]. The safety profile of any treatment is, therefore, an important consideration when choosing a therapeutic option in this setting[4]. In clinical practice, patients with moderate to severe psoriasis are often prescribed combinations of a biologic agent plus a conventional systemic drug, usually methotrexate (MTX).[5–7] Although the safety of combination regimens in the treatment of other inflammatory diseases, such as rheumatoid arthritis, has been assessed, there is little evidence on their use in patients with psoriasis[6], especially for the combination regimens with the most modern biologics (the interleukin [IL] 17 and IL-23 antagonists)[8]. It is important to stress that safety data for biologic drugs in other inflammatory diseases should not be extrapolated to patients with psoriasis, as the risks of adverse events can be very different[9,10].

It is, therefore, essential to characterise the safety profile of regimens combining MTX with biologic agents in patients with moderate to severe psoriasis.

The objectives of this study were: (a) To describe the characteristics of patients who have received combined therapy; (b) To identify the most common AEs in each treatment group; and (c) to ascertain whether the use of regimens combining biologic drugs with MTX in the management of moderate to severe psoriasis increases the risk of adverse events (AEs) or serious AEs (SAEs).

Monotherapy was compared to the combination regimen for each class of biologic therapy (tumour necrosis factor [TNF] agents and IL-17 and IL-23 antagonists).

MATERIALS AND METHODS

The data analysed came from the Spanish Registry of Systemic Treatments in Psoriasis (BIOBADADERM), a registry created to monitor the AEs and SAEs associated with systemic therapy. A detailed description of how this data is collected and codified has been published previously[4,11]. BIOBADADERM is a national, prospective multicentre cohort registry of patients with psoriasis in clinical practice and all patients treated with systemic drugs at participating hospitals are invited to enter the cohort. BIOBADADERM included all patients registered from 18 tertiary dermatology departments. The study period spans from January 2008 through November 2021.

To describe long-term safety, data on AEs was collected using the Medical Dictionary for Regulatory Activities (MedDRA). SAEs were defined in agreement with the International Conference on Harmonisation[12]. All SAEs or AEs that led to a change in therapy or an unplanned health event were included. The time of exposure to a systemic drug was recorded from the date of start of treatment to the date of last administration or the censor date in patients lost to follow-up. The censor date in patients lost to follow-up was the last visit to the dermatologist.

BIOBADADERM is continuously monitored online, and the data is validated once a year through on-site audits. The registry was approved by the Hospital 12 de Octubre Ethics Committee (216/07) and its operation complies with the Declaration of Helsinki. All patients sign informed consent to participate.

Study groups and outcomes

In the analysis, patients were divided into 3 categories according to the class of biologic agent they received: TNF inhibitors (etanercept, infliximab or adalimumab and their biosimilars, certolizumab and golimumab); IL-23 inhibitors (ustekinumab, tildrakizumab, guselkumab and risankizumab); or IL-17 inhibitors (secukinumab, ixekizumab and brodalumab). Patients were defined as recipients of combined therapy if they received a biologic agent plus MTX for more than 2 months (overlap ≥ 2 months). Combinations of a biologic agent with other conventional systemic drugs, such as ciclosporin and acitretin, was uncommon, and these patients were all excluded, as were patients who received MTX alone. Combined therapy was analysed as both a binary variable (yes/no) and a continuous variable (total time of combined therapy). The unit of analysis was one treatment cycle, which means that a patient could receive more than one treatment over time and could belong to more than one group. Adverse events were linked to a therapy if they took place since the start of the therapy to 90 days after its end. We excluded those patients who enrolled in the registry recently (less than 90 days of follow-up) because they didn't have the chance to spend 90 days after treatment initiation. Patients aged below 18 years were also excluded (Figure 1).

Primary outcome: the adjusted incidence rate ratios for total AEs, SAEs, and specific system organ class AEs between patients receiving combined therapy with methotrexate and those not receiving it. An AE was considered to be associated with a therapy if it occurred from the start of the therapy up to 90 days after its conclusion.

Three group comparisons were performed. The first group compared TNF inhibitors monotherapy versus combined TNF inhibitors and MTX. The second group compared IL-23 inhibitors monotherapy versus combined IL-23 inhibitors and MTX. The third group compared IL-17 inhibitors monotherapy versus combined IL-17 inhibitors and MTX.

Statistical analysis

Descriptive data were expressed as absolute numbers and percentages for discrete variables and as medians and interquartile ranges for continuous skewed variables.

A few variables had missing values, ranging from 0.5% (disease duration) to 26.4% (alcohol consumption). We used multiple imputation to manage missing values. We created 20 complete datasets by means of chained equations, based on the assumption that missing values were missing at random, using a fully conditional specification model[13]. We examined imputed values against iteration to assess the convergence and

stationarity of each chain. In further steps, the 20 datasets were analysed using a random effects Poisson regression. Finally, the results of the complete datasets were combined into a single set of estimates using the Rubin rules[14].

We estimated adjusted incidence rate ratios (aIRR, similarly interpreted as risk ratios[RR]) and incidence rate differences (similarly interpreted as risk differences), including 95% confidence intervals (CI), for all AEs, SAEs, fatal events and each MedDRA system organ class group, comparing monotherapy and combined therapy. A rate ratio is a measure used to compare the incidence rates of events between two groups. The rate difference, on the other hand, refers to the incidence rate of a disease that can be attributed to a specific exposure—in our case, MTX—assuming a causal relationship, and helps to describe the clinical relevance of the findings in absolute terms.

Only MedDRA categories with more than 80 AE in total were presented (except for fatal events and serious infections events) to allow for robust estimations. We described incidence rates of adverse events per 1,000 patient-years of exposure with 95% CI by period. For aIRR, we used a random effects Poisson with robust variance regression model to account for overdispersion and correlated data. We included age, sex, BMI, psoriatic arthritis, prior biologic treatment, and dermatology department in the final model as the main confounding variables. These were selected based on clinical knowledge and as significant confounders identified in previous studies[4,10]. All confounders were measured at baseline.

All analyses were performed using STATA v.17.0 (Stata Corp. 2021. Stata Statistical Software: Release 17). A *P* value (adjusted with Bonferroni correction for multiple comparisons) of less than 0.002 was considered statistically significant. Results are presented with one decimal, when necessary, except for aIRR which are shown with two decimal places.

RESULTS

We analysed data from 2,829 patients and 5,441 treatment cycles, a total of 12,853 patient-years. Of these, 516 cycles (9.5%) were combined therapy with MTX, and 4,925 cycles (90.5%) were monotherapy with TNF (50.3%), IL-17 (30.5%) or IL-23 inhibitors (19.2%).

Patient Characteristics

Patient characteristics are summarised by treatment group in Table 1. TNF inhibitors were the most frequently prescribed drug type. The most common combination regimen was MTX plus a TNF inhibitor, followed by MTX with an IL-23 and then with an IL-17 inhibitor.

The majority of the patients were men, and the most common diagnosis was plaque psoriasis. In all the groups, patients who received combined therapy had a higher

percentage of psoriatic arthritis (PsA) and had more often received prior biologic therapy than those receiving biologics alone, except in the case of the TNF group, in which the percentages were similar. By contrast, the prevalence of comorbidities and severity at start of treatment (measured using the Psoriasis Area and Severity Index [PASI]) were similar for both the monotherapy and combined therapy groups, except for renal insufficiency and chronic liver disease, which were present in almost none of the patients on combined regimens.

Characteristics of AEs associated with biologic and MTX combined regimens

In total, 7,230 AEs were reported, including 680 SAEs (9.4%), with a fatal outcome in 0.6% of cases (n=40). Of these, 6,137 were associated with biologic monotherapy (84.9%) and 1,093 occurred in patients on combined therapy with MTX (15.1%).
The incidence rates of infections without methotrexate range from 105 cases (95% CI: 96-116) per 1000 person-years in the IL-23 group, to 140 (95% CI: 124-158) in the IL-17 group. Detailed information on AEs can be found in Table 2. We did not describe in the results those AEs with a too low incidence (n<80) in order to permit robust rate estimations.
While the patients on combined regimens had a higher incidence of AEs overall, the difference was not statistically significant. For SAEs, numerically the incidence was almost the same and there was no statistical difference between the groups.
The same trend was observed in the most reported AEs, infections and infestations (n=1,617, of which 7.1% were serious). The next most frequently reported AEs, in descending order, were musculoskeletal and connective tissue diseases, abnormal laboratory values, skin and subcutaneous tissue disorders, and gastrointestinal intolerance.

Adjusted incidence rate ratios and rate differences of AEs for combined therapy and monotherapy

The detailed results are shown Tables 3 and 4. In general, MTX combined therapy was not associated with a statistically significant increase in the risk of AEs or SAEs.
An increase in gastrointestinal AEs was observed for the combination of MTX with TNF, IL-23 and IL-17 inhibitors, but was statistically significant only in the case of the TNF inhibitors (aIRR=2.50; 95% CI 1.57–3.98). A statistically non-significant increase in musculoskeletal and connective tissue AEs was observed for combined therapy with IL-23. No increase in total infections or serious infections was detected in patients on combined therapy.
Rate ratios are lower overall in patients who have been on treatment for over a year.
The attributable risk of total AEs and SAEs in terms of risk difference for combined treatment as compared to monotherapy is shown in Table 4. Regimens combining MTX and a TNF inhibitor were associated with 18 (95% CI, 4–33) more gastrointestinal AEs per 1000 person-years of exposure.

DISCUSSION

Overall, combined regimens with MTX were not associated with any statistically significant increase in the risk of AEs or SAEs with respect to biologic monotherapy. In the analysis of specific AEs, no increased risk of total infections or serious infections was observed in the patients on combined therapy. An increase in gastrointestinal AEs was observed in association with the combination of MTX plus a TNF inhibitor.

The data from our study show that biologic treatments were combined with MTX in approximately 10% of treatment cycles studied. This is a somewhat higher proportion than that reported by Busard et al[6] in 5 PSONET registries, in which MTX was combined with biologics in only 7.2% of patients. However, it is lower than the percentages reported by Iskandar et al[5] for the British Association of Dermatologists Biologic Interventions Register (BADBIR) and by Penso et al[7] in a study of data from the French National Health Data System, in which this combination was used in 15.4% and 15.1% of patients, respectively.[5,7] These findings show that combined therapy is relatively common in current clinical practice, despite the paucity of evidence for its safety in psoriasis. In all those studies, MTX was the systemic drug most frequently used in combined therapy. In our study, patients on combination regimens did not have more severe psoriasis than those receiving biologic monotherapy; this is in line with the findings of the Corrona Psoriasis Registry[15] but not with data from other registries[6,7]. However, like in all previous studies, joint involvement was more frequent in the patients on combined treatment, an indication that its presence in patients with psoriasis is one of the main motives for the prescription of combined therapy since joint disease is less responsive to biologic monotherapy than cutaneous symptoms.

We detected no significant differences in the rates of AEs or SAEs, a finding consistent with the results of several clinical trials that have reported no increase in the rate of AEs when MTX is added to treatment with TNF[16-19] or IL-17[19,20] inhibitors in patients with psoriasis. However, some authors have reported a higher rate of AEs in combined therapy groups[21–24]. It should be noted that these earlier studies, unlike ours, did not directly compare the two groups. A meta-analysis by Xie et al, which compared the safety profile of a combination regimen with a TNF inhibitor to biologic monotherapy in patients with psoriasis, evidenced a slight increase in the rate of total AEs for combined therapy as compared to monotherapy (RR=1.21; 95% CI, 1.13−1.30), although with a moderate level of heterogeneity between studies for this outcome (I^2=66%). However, as in our study, those authors observed no significant differences between the two groups in the number of SAEs (RR=0.71; 95% CI, 0.42−1.20; P = 0.20)[25].

Our data do not show any increased risk of total or serious infections in patients on combined treatment with MTX plus any of the classes of biologic agents studied. In a previous study of data from the BIOBADADERM registry, a tendency was observed toward an increase in the rate and relative risk of serious infections in all the regimens combining biologics and methotrexate, compared with monotherapy with the same

biologic[10]. However, the sample size for patients on combined treatment was much smaller and these results have not been confirmed by the present study based on a larger sample.

In the present study, an increased risk of gastrointestinal AEs was observed during the first year of treatment with the combination of a TNF inhibitor plus MTX (aIRR: 2.50). In clinical terms, this combination resulted in 19 more gastrointestinal AEs per 1000 person-years of exposure. This increased risk is to be expected because gastrointestinal symptoms are the AE most frequently associated with MTX. This result may also be influenced by the fact that most of our patients received oral MTX (74%) and it is possible that tolerance could be improved with subcutaneous administration[26]. Inclusion of a group treated with methotrexate monotherapy would have provided insights into the baseline risk.

For the other AEs analysed, an increased risk (not statistically significant) was observed in musculoskeletal and connective tissue AEs during the first year of treatment in patients who received combined therapy with IL-23 antagonists (aIRR: 1.72). It could be attributed to a possible worsening of joint symptoms when the patient switched to a different class of biologic therapy from those more often used in PsA (TNF or IL-17 inhibitors)[27].

Given the observational nature of this study, one limitation is the potential for selection bias in either prescription or follow-up. The patients treated with combined therapy may have been chosen because they had a low risk of developing AEs. Additionally, survival bias may affect our findings, as patients more prone to complications may tend to abandon combined treatment, which could explain why AE rates decrease after the first year of treatment. Immortal time bias is another potential issue if the start of follow-up for combined therapy patients is marked from the commencement of biologic therapy, even if combination therapy is initiated later. Despite these potential sources of bias, the data are representative of how many participants are currently treated, so it can be generalised to routine clinical practice.

It should be noted that changing trends over the life of the registry in the types of treatments administered could mean that the profile of patients currently receiving combined treatment may not be similar to that of patients who received it in earlier years[28]. Likewise, drugs such as infliximab, which are associated with a higher percentage of AEs and SAEs than other biologics[4], are no longer commonly prescribed in this setting but are included in the anti-TNF group in our study.

The failure to detect differences could be due to the low statistical power because of the low number of AEs, especially serious infections. However, the fact that the 95% CIs of the risk ratios reported are not very wide and the AEs are infrequent means that the results do not reflect risks of any significant clinical impact. The risk difference results are useful in evaluating this limitation, which may apply particularly to the smaller patient groups.

The study also has several strengths: its prospective design; the quality of the data in the BIOBADADERM registry, which has a continuous data monitoring system (an unusual characteristic in observational studies); the relatively large sample comprising patients from different hospitals across Spain; the industry-independent data analysis; and the inclusion of new systemic drugs not included in some other registries. The inclusion of new types of biologics used in psoriasis provides valuable data on current clinical practice.

In short, our study has shown that the combination of MTX with TNF, IL-17 and IL-23 inhibitors in patients with moderate to severe psoriasis does not significantly increase the risk of AEs, SAEs or infections compared to monotherapy with the same biologic drugs. Consequently, the safety profile should not be a limitation when combined therapy is considered useful, for example in patients who have an inadequate response to monotherapy or comorbidities such as PsA. Combined regimens can also be useful as a bridging treatment or as an intermittent therapy in patients who experience flares[29].

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Table 1: Patients' characteristics.

	TNF	**TNF+MTX**	**p-value**	**IL-23**	**IL-23+MTX**	**p-value**	**IL-17**	**IL-17+MTX**	**p-value**
Demographic data									
Number of patients‡	1,562	238		1,151	114		784	89	
Patient-years	5,235	986		4,051	502		1,836	244	
Number of cycles	2,476	285		1,501	127		948	104	
Mean time of exposure, years (SD)	2.1 (2.7)	3.5 (3.1)	**<0.002**	2.7 (2.8)	4 (3.3)	**<0.002**	1.9 (1.4)	2.3 (1.4)	**<0.002**
Mean time on combined treatment, months (SD)	0	20 (21)		0	21 (23)		0	18 (16)	
Time on combined therapy									
2 months–1 year, n (%)	0 (0)	153 (54)		0 (0)	65 (51)		0 (0)	51 (49)	
>1 year, n (%)	0 (0)	132 (46)		0 (0)	62 (49)		0 (0)	53 (51)	
Women, n (%), missing (0)	642 (41)	93 (39)	0.554	496 (43)	50 (44)	0.875	332 (42)	39 (44)	0.790
Mean age, years (SD), missing (0)	53 (14)	54 (13)	0.141	53 (14)	54 (14)	0.621	53 (13)	56 (11)	0.015
Mean age at start of treatment, years (SD), missing (0)	46 (14)	46 (13)	0.996	48 (14)	48 (14)	0.571	50 (13)	53 (11)	0.052
Mean disease duration at start of treatment, years (SD), missing (16)	19 (13)	21 (12)	0.073	21 (13)	22 (13)	0.164	19 (13)	24 (12)	0.002
Mean PASI (SD), missing (262)	10 (9)	10 (9)	0.586	11 (8)	11 (7)	0.845	9 (8)	9 (9)	0.644
Mean BMI (SD), missing (545)	28 (6)	29 (6)	0.156	28 (6)	30 (6)	0.037	29 (7)	30 (6)	0.459
Diagnosis on registration, n (% of total)									
Plaque psoriasis, missing (0)	1,437 (92)	225 (95)	0.170	1,182 (94)	108 (95)	0.752	727 (93)	80 (90)	0.337
Guttate psoriasis, missing (0)	74 (5)	3 (1)	0.014	47 (4)	4 (4)	0.766	31 (4)	1 (1)	0.178
Erythrodermic psoriasis, missing (0)	23 (1)	5 (2)	0.466	21 (2)	2 (2)	0.957	12 (2)	6 (7)	**<0.002**

Generalised pustular psoriasis, missing (0)	13 (1)	4 (2)	0.208	12 (1)	2 (2)	0.488	5 (1)	2 (2)	0.107
Palmoplantar pustulosis, missing (0)	39 (2)	3 (1)	0.239	25 (2)	2 (2)	0.767	40 (5)	5 (6)	0.835
Annular pustular psoriasis, missing (0)	3 (0)	1 (0)	0.486	2 (0)	1 (1)	0.141	3 (0)	0 (0)	0.559
Acrodermatitis continua of Hallopeau, missing (0)	2 (0)	0 (0)	0.581	0 (0)	0 (0)	0.910	1 (0)	0 (0)	0.736
Psoriatic arthritis, missing (0)	279 (18)	76 (32)	**<0.002**	147 (13)	37 (32)	**<0.002**	163 (21)	37 (42)	**<0.002**
Comorbidities, n (% of total)									
Ischaemic heart disease, missing (385)	35 (2)	6 (3)	0.833	34 (3)	3 (3)	0.731	21 (3)	3 (4)	0.591
Heart failure, missing (398)	7 (1)	2 (1)	0.470	14 (1)	1 (1)	0.686	5 (1)	1 (1)	0.589
Arterial hypertension, missing (287)	309 (22)	53 (24)	0.539	249 (24)	31 (28)	0.391	179 (26)	27 (33)	0.150
Diabetes, missing (335)	182 (13)	29 (13)	0.995	144 (14)	11 (10)	0.250	95 (14)	10 (13)	0.744
Hypercholesterolemia, missing (302)	396 (28)	65 (29)	0.808	293 (28)	35 (31)	0.517	245 (35)	26 (33)	0.619
COPD, missing (396)	36 (3)	2 (1)	0.118	34 (3)	2 (2)	0.378	24 (4)	2 (3)	0.658
Chronic liver disease, missing (382)	127 (9)	10 (5)	0.021	86 (9)	3 (3)	0.033	94 (14)	3 (4)	0.012
Renal insufficiency, missing (394)	27 (2)	1 (0)	0.110	24 (2)	0 (0)	0.103	11 (2)	0 (0)	0.258
Prior cancer, missing (395)	25 (2)	5 (2)	0.657	41 (4)	7 (6)	0.253	30 (4)	5 (6)	0.424
Cancer in the preceding 5 years, excluding non-melanoma skin cancer, missing (399)	0 (0)	0 (0)	NA	2 (0)	1 (1)	0.167	4 (1)	0 (0)	0.499
Lymphoma, missing (413)	2 (0)	0 (0)	0.571	3 (0)	0 (0)	0.568	2 (0)	0 (0)	0.633
Hepatitis B†, missing (332)	15 (1)	0 (0)	0.262	12 (1)	0 (0)	0.194	6 (1)	0 (0)	0.158
Hepatitis C†, missing (329)	12 (1)	0 (0)	0.153	12 (1)	0 (0)	0.151	7 (1)	0 (0)	0.637
HIV†, missing (464)	29 (2)	1 (1)	0.169	16 (2)	0 (0)	0.285	18 (3)	1 (1)	0.476
Prior biologic treatments, n (% of total)									
Prior biologic treatments, yes, missing (0)	1,279 (52)	146 (51)	0.891	1,113 (74)	103 (81)	0.084	711 (75)	92 (88)	0.002

Number of prior biologic treatments, missing (0)			0.614			0.058			0.003
0	1,197 (48)	139 (49)		388 (26)	24 (19)		237 (25)	12 (12)	
1	645 (26)	64 (22)		465 (31)	48 (38)		274 (29)	25 (24)	
2	295 (12)	41 (14)		305 (20)	25 (20)		184 (19)	24 (23)	
3	155 (6)	19 (7)		145 (10)	19 (15)		93 (10)	17 (16)	
4 or more	184 (7)	22 (8)		198 (13)	11 (9)		160 (17)	26 (25)	

‡ The total number of patients reported for each group does not equal the total number of patients in the study because some patients belong to more than one treatment group.

† Percentage of positive results in patients in whom the prior test was done.

MTX, methotrexate; PASI, Psoriasis Area Severity Index; BMI, Body Mass Index; COPD Chronic Obstructive Pulmonary Disease; SD, standard deviation.

P value ($P<0.002$) adjusted for multiple comparisons.

Table 2. Adverse events incidence rates.

	TNF		**TNF + MTX**		**IL-23**		**IL-23 + MTX**		**IL-17**		**IL-17 + MTX**	
Number of person-years of exposure	**5235**		**986**		**4051**		**502**		**1836**		**244**	
	Number of events	Incidence per 1000 person-years (95% CI)	Number of events	Incidence per 1000 person-years (95% CI)	Number of events	Incidence per 1000 person-years (95% CI)	Number of events	Incidence per 1000 person-years (95% CI)	Number of events	Incidence per 1000 person-years (95% CI)	Number of events	Incidence per 1000 person-years (95% CI)
All adverse events	3234	618 (597–639)	662	672 (622–725)	1854	458 (437–479)	273	544 (483–613)	1049	571 (538–607)	158	648 (554–757)
Serious adverse events	311	59 (53–66)	61	62 (48–80)	190	47 (41–54)	17	34 (21–54)	96	52 (43–64)	5	20 (9–49)
Fatal adverse events	17	3 (2–5)	3	3 (1–9)	15	4 (2–6)	1	2 (0–14)	3	2 (1–5)	1	4 (1–29)
Infections and infestations (SAE)	44	8 (6–11)	8	8 (4–16)	31	8 (5–11)	4	8 (3–21)	26	14 (10–21)	2	8 (2–33)
Infections and infestations (ALL)	707	135 (125–145)	142	144 (122–170)	427	105 (96–116)	61	122 (95–156)	257	140 (124–158)	23	94 (63–142)
Skin and subcutaneous tissue disorders	243	46 (41–53)	51	52 (39–68)	113	28 (23–33)	21	42 (27–64)	78	42 (34–53)	12	49 (28–87)
Gastrointestinal disorders	169	32 (28–37)	50	51 (38–67)	96	24 (19–29)	16	32 (20–52)	57	31 (24–40)	14	57 (34–97)
Investigations (laboratory abnormalities)	304	58 (52–65)	68	69 (54–87)	165	41 (35–47)	20	40 (26–62)	90	49 (40–60)	16	66 (40–107)
Musculoskeletal and connective tissue disorders	306	58 (52–65)	57	58 (45–75)	194	48 (42–55)	32	64 (45–90)	123	67 (56–80)	22	90 (59–137)

Table 3 Adjusted incidence rate ratios (length of exposure in categorical values)*.

System Organ Classes (SOCs)	TNF	IL-23	IL-17
Combined with MTX	Adjusted IRR (95% CI)	Adjusted IRR (95% CI)	Adjusted IRR (95% CI)
All adverse events			
Not combined	Ref	Ref	Ref
2 months−1 year	1.19 (0.96–1.48)	1.08 (0.74–1.57)	1.36 (0.97–1.91)
>1 year	**0.74 (0.62–0.88)** ‡	0.91 (0.69–1.19)	0.81 (0.53–1.25)
Serious adverse events (SAE)			
Not combined	Ref	Ref	Ref
2 months−1 year	0.88 (0.50–1.56)	0.22 (0.08–0.59)	0.31 (0.08–1.15)
>1 year	0.87 (0.55–1.36)	0.75 (0.39–1.44)	0.23 (0.08–0.70)
Fatal adverse events			
Not combined	Ref	Ref	Ref
2 months−1 year	0.77 (0.07–8.99)	NA	NA
>1 year	0.93 (0.12–7.44)	1.39 (0.01–276.14)	NA
Infections and infestations (SAE)			
Not combined	Ref	Ref	Ref
2 months−1 year	0.96 (0.26–3.50)	NA	0.81 (0.09–7.38)
>1 year	0.64 (0.16–2.68)	1.53 (0.42–5.61)	0.25 (0.03–1.86)
Infections and infestations (ALL)			
Not combined	Ref	Ref	ref
2 months−1 year	1.28 (0.93–1.75)	0.58 (0.35–0.98)	1.15 (0.63–2.09)
>1 year	0.85 (0.64–1.11)	1.01 (0.63–1.62)	0.39 (0.19–0.83)
Skin and subcutaneous tissue disorders			
Not combined	Ref	Ref	ref
2 months−1 year	1.40 (0.84–2.34)	1.06 (0.47–2.42)	1.21 (0.38–3.86)
>1 year	0.83 (0.53–1.29)	1.60 (0.93–2.76)	1.02 (0.46–2.26)
Gastrointestinal disorders			
Not combined	Ref	Ref	Ref
2 months−1 year	**2.50 (1.57–3.98)** ‡	1.00 (0.42–2.36)	2.62 (1.08–6.35)
>1 year	1.18 (0.74–1.88)	1.27 (0.56–2.91)	1.15 (0.16–8.17)
Investigations			
Not combined	Ref	Ref	ref
2 months−1 year	1.30 (0.85–2.00)	1.25 (0.45–3.43)	1.95 (0.72–5.24)
>1 year	0.71 (0.43–1.19)	1.03 (0.42–2.52)	0.87 (0.35–2.16)
Musculoskeletal and connective tissue disorders			
Not combined	Ref	Ref	ref

2 months−1 year	0.94 (0.58–1.53)	1.72 (0.97–3.07)	1.43 (0.70–2.90)
>1 year	0.95 (0.63–1.44)	0.82 (0.45–1.50)	1.04 (0.53–2.05)

*Adjusted by age, sex, BMI, previous biologic treatments, hospital and psoriatic arthritis.

‡ P value (P<0.002) adjusted for multiple comparisons.

Table 4: Attributable risk for AEs in patients on combined therapy with MTX compared to monotherapy in terms of risk difference.

	TNFα	IL-23	IL-17
System Organ Classes (SOCs)	**Combined with MTX**	**Combined with MTX**	**Combined with MTX**
	Risk Difference per 1000 person-years (95% CI)	Risk Difference per 1000 person-years (95% CI)	Risk Difference per 1000 person-years (95% CI)
All adverse events	54 (-2–109)	86 (19–154)	76 (-30 to 183)
Serious adverse events	2 (-14 to 19)	-13 (-30 to 4)	-32 (-53 to -11)
Fatal adverse events	0 (-4 to 4)	-2 (-6 to 3)	2 (-6 to 11)
Infections and infestations (SAE)	0 (-6 to 6)	0 (-8 to 9)	-6 (-19 to 7)
Infections and infestations (ALL)	9 (-17 to 35)	16 (-16 to 48)	-46 (-88 to -3)
Skin and subcutaneous tissue disorders	5 (-10 to 21)	14 (-5 to 33)	7 (-23 to 36)
Gastrointestinal disorders	18 (4–33)	8 (-8 to 24)	26 (-5 to 57)
Investigations	11 (-7 to 29)	-1 (-19 to 18)	17 (-17 to 50)
Musculoskeletal and connective tissue disorders	-1 (-17 to 16)	16 (-7 to 39)	23 (-16 to 63)

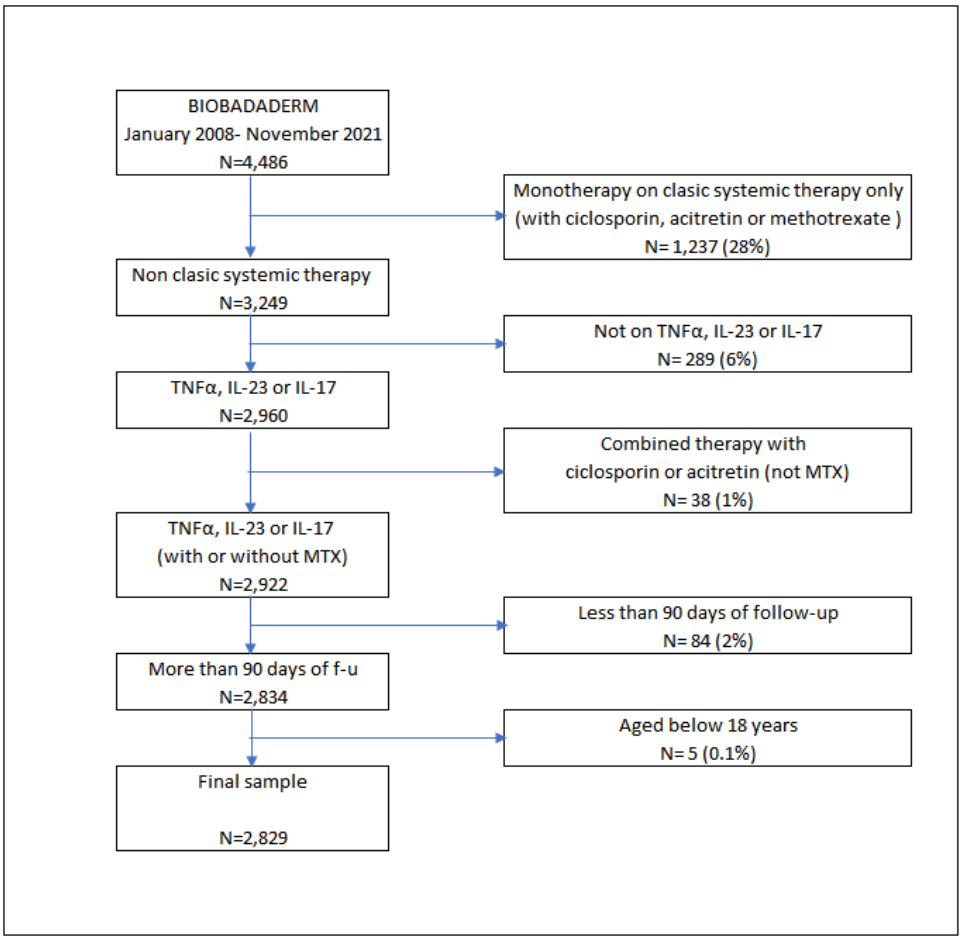

Figure 1: STROBE diagram depicting the participant flow in the study.