Failure of first anti-TNF agent in Takayasu's arteritis: to switch or to swap?

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Received on September 26, 2020; accepted in revised form on November 23, 2020.

Clin Exp Rheumatol 2021; 39 (Suppl. 129): S129-S134.

Key words: Takayasu's arteritis, biologic, refractory, TNF-alpha, tocilizumab, failure

This study was approved in compliance with the Pan-immuno protocol approved by the Institutional Ethics Committee (registry number: 22/INT/2018).

Competing interests: page S133.

ABSTRACT

Objective. *Biologic drugs (bDMARD), especially TNF-α-inhibitors (TNFi), are used in refractory Takayasu's arteritis (TAK) patients. Up to 23% of patients are switched to a different b-DMARD because of inefficacy. No data are available on which strategy is more efficient after TNFi failure. The aim of our study is to evaluate whether a* switch *or* swap *strategy should be preferred in TAK patients failing TNFis.*

Methods. *TAK patients treated with a second bDMARD after the failure of the first TNFi were identified from 3 referral centres. Patients were classified as switch if treated with a different TNFi, and* swap *if treated with a non-TNFi bDMARD. Baseline features were evaluated. Efficacy and safety of the second bDMARD at 6 and 12 months were assessed and a comparison between* switch *and* swap *patients was made.*

Results. *Twenty-four TAK patients were identified. Eleven patients (46%) were* switched *and 13 patients (54%) were* swapped *(12 to tocilizumab, 1 to ustekinumab). Baseline features of patients in the 2 groups were comparable. At 12 months, the second bDMARD was suspended in 4* switch *(36%) and in 5* swap *(42%) patients. Second biologic drug survival and relapse-free survival were equivalent between the two groups at 6 and 12 months. A vascular worsening was observed in 4* switch *(40%) and 2* swap *(25%) patients. Severe infections, myocardial infarction, ischaemic stroke or cancer were recorded in no patient.*

Conclusions. *Our retrospective study suggests that in first-line TNFi failure TAK patients both* switch *and* swap *strategies can be considered suitable approaches.*

Introduction

Takayasu's arteritis (TAK) is a chronic granulomatous large-vessel vasculitis mainly affecting young women (1, 2). The goal of medical treatment in TAK patients is to control vascular inflammation in order to avoid irreversible vascular damage that can lead to both stenotic and aneurysmatic lesions (3-5). Steroid therapy represents the first-line treatment option of TAK patients, with a generally favourable response (6). Unfortunately, upon steroid tapering, up to 50% of patients can experience a flare and require the addition of a conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) (3, 7). In the case of refractory or relapsing disease, the immunosuppressive therapy is further escalated with the introduction of a biologic DMARD (bDMARD) (8, 9).

While several classes of bDMARD have been used in TAK patients (10), TNF-α inhibitors (TNFi), mainly infliximab, and the anti-IL-6 receptor antagonist tocilizumab are considered the most effective therapeutic options (11, 12). However, no data are available on the outcome of TAK patients failing a first-line TNFi and which treatment strategy should be adopted in this context. Similarly to other rheumatic diseases (13), the question is then whether to prefer the use of a bDMARD with a different mechanism of action or cycling to another TNFi.

The aim of this multicentre retrospective study is to investigate the 12-month outcome of TAK patients who failed a first-line TNFi therapy according to their second-line bDMARD therapy: patients treated with a different TNFi (*switch* group), and patients treated with a non-TNFi biologic drug (*swap* group).

Methods

Study population

Data from TAK patients treated with biologic agents followed-up at three Italian referral hospitals for vasculitis (IRCCS San Raffaele Hospital, Milan, Azienda USL-IRCCS di Reggio Emilia, Gianna Gaslini Hospital, Genova) were retrospectively evaluated. All patients fulfilled the 1990 American College of Rheumatology Criteria (14). Among these patients, those treated with a TNFi as first-line biologic therapy and eventually treated with a different biologic agent were identified. Any of the five currently available TNFi was considered (*i.e.* infliximab, adalimumab, etanercept, golimumab, certolizumab pegol). Patients were classified according to the different therapeutic strategy adopted after first TNFi-failure: patients who were treated with a different TNFi (switch group), and patients who were treated with a non-TNFi biologic drug (swap group).

Study assessments

Disease features at second biologic drug start were evaluated. These included demographics, TAK duration, extension of vascular involvement, disease activity, reason for first-line TNFi failure, and concomitant therapies. Extension of vascular involvement was classified according to the angiographic criteria proposed by Hata *et al.* (15), whereas disease activity was graded using the score created by Kerr *et al.* (NIH score) (1).

Efficacy and safety of the second biologic drug, percentage of second biologic failure, reasons of failure, and changes in the concomitant immunosuppressive drugs were assessed at 6 and 12 months from its start, and a comparison between the two groups (switch and swap) was made. Efficacy was assessed through evaluation of the number of relapses and need for vascular interventions. Relapse was defined as NIH score ≥2 with consequent therapy modification. When available, the degree of vascular involvement, evaluated by comparing magnetic resonance angiography (MRA) evolution over time, was also assessed.

Adverse events, in particular incidence of vascular complications (*i.e.* myocardial infarction, ischaemic stroke), cancer and severe infections (defined as infections requiring hospital admission), were assessed at 6 and 12 months after second biologic agent introduction.

Statistical analysis

Data were analysed using SPSS 24.0 (SPSS, Chicago, IL). Categorical variables were reported as numbers and percentage, whereas continuous variables were reported as the median and interquartile ranges (IQR). Two-tailed Fisher's exact test and Mann-Whitney U test were used for statistical comparison. Survival analysis was performed with the Kaplan-Meier approach; comparison between survival curves was performed with the log-rank test. Statistical significance was defined as a p-value <0.05.

Table I. Demographic and clinical features at second biologic drug start of patients with Takayasu arteritis first treated with an anti-TNF-α and then switched to another anti-TNF-α or swapped to a biologic drug with a different mechanism of action.

Variable	Switch patients (n=11)	Swap patients (n=12)	p-value
Age, years (mean ± SD)	32.3 ± 17.1	32.3 ± 12.8	1
Female sex, n (%)	9 (82)	12 (100)	0.22
Disease duration, months (mean ± SD)	69.1 ± 64.5	61.2 ± 44.4	0.83
Length of first TNFi therapy, months (mean ± SD)	30.1 ± 29.3	29.3 ± 24.8	0.92
Vascular involvement, type V[15] (%)	5 (45)	6 (50)	1
NIH score ≥ 2[1], n (%)	8 (73)	7 (58.3)	0.67
Prednisone equivalent daily dose, mg (mean ± SD)	16.1 ± 10.3	17.9 ± 15	0.13
Concomitant csDMARD, n (%)	10 (91)	9 (75)	0.59
C-reactive protein, mg/L (mean ± SD)	45.5 ± 31	28 ± 28.7	0.1
Erythrocyte sedimentation rate, mm/h (mean ± SD)	44.1 ± 22.2	50.6 ± 22	0.41

csDMARD: conventional synthetic disease-modifying antirheumatic drug; SD: standard deviation; TNFi: anti-TNF-α.

Results

Baseline characteristics

A total of 98 TAK patients treated with at least one bDMARD were identified. Among them, 24 patients failed a first-line treatment course with a TNFi. Five of them (21%) were ≤18 years of age, and therefore were diagnosed with childhood TAK (16). The first-line TNFi was infliximab in 13 cases (54%), adalimumab in 8 (34%), golimumab in 2 (8%), and etanercept in 1 (4%). No patient was initially started on certolizumab pegol. The first-line TNFi was withheld after a median of 19 (8.5–38) months, in 9 patients (37%) within 12 months after introduction. Reasons for first-TNFi suspension were inefficacy in 19 patients (79%) and side effects in 5 patients (21%).

A second TNFi was started in 11 patients (46%, *switch* group), whereas in 13 patients (54%) an agent with a different mechanism of action was preferred (*swap* group). The second TNFi was infliximab and adalimumab in 4 cases each, golimumab in 2, and etanercept in 1. In the *swap* group, the second biologic agent was tocilizumab in all patients except for one who was treated with ustekinumab. One patient of the *swap* group, originally treated with adalimumab and then started on tocilizumab, was excluded from the analysis as he was lost on follow-up.

At second biologic initiation, demographic and clinical features were comparable between the two groups (Tables I and II). All patients were on concomitant therapy with systemic glucocorticoids, with the exception of one patient in the *swap* group. In 10 *switch* (91%) and in 9 *swap* (75%) patients the second biologic agent was combined with a csDMARD (mostly, methotrexate).

Drug retention and disease activity

At 6 months, the second biologic drug was suspended in a total of 6 patients (23%): 3 patients (27%) in the *switch* group and 3 patients (25%) in the *swap* group. At 12 months, this number increased to a total of 9 (39%) patients: 4 (36%) in the *switch* and 5 (42%) in the *swap* group. Second biologic drug survival was equivalent between the two groups at both time points (Fig.

Table II. Immunosuppressive therapy modifications in 23 patients with Takayasu's arteritis first treated with an anti-TNFα and then switched to another anti- TNFα or swapped to a biologic drug with a different mechanism of action.

		Baseline			6 months			12 months		
	First bDMARD	Second bDMARD	csDMARD	Prednisone	Second bDMARD	csDMARD	Prednisone	Second bDMARD	csDMARD	Steroid dose
***Switch* 1**	IFX 7 mg/kg q6w	ADA 40 mg q2w	MTX 20 mg/w	15 mg daily	ADA 40 mg wkly	MTX 20 mg/w	5 mg daily	ADA 40 mg wkly	MTX 20 mg/w	5 mg daily
***Switch* 2**	IFX 5 mg/kg q8w	ADA 40 mg q2w	MMF 2 g daily	15 mg daily	ADA 40 mg q2w	MMF 2 g daily	8,75 mg daily	-	-	-
***Switch* 3**	IFX 5 mg/kg q4w	ADA 40 mg q2w	CYC 100 mg daily	40 mg daily	-	-	-	-	-	-
***Switch* 4**	IFX 5 mg/kg q8w	ADA 40 mg q2w	MTX 15 mg/w	25 mg daily	ADA 40 mg q2w	MTX 15 mg/w	15 mg daily	ADA 40 mg q2w	MTX 15 mg/w	15 mg daily
***Switch* 5**	IFX 5 mg/kg q8w	ETN 50 mg wkly	-	15 mg daily	-	-	-	-	-	-
***Switch* 6**	IFX 10 mg/kg q6w	GOL 50 mg q4w	MTX 20 mg/w	7,5 mg daily	GOL 50 mg q4w	MTX 20 mg/w	5 mg daily	GOL 50 mg q4w	MTX 20 mg/w	5 mg daily
***Switch* 7**	IFX 10 mg/kg q5w	GOL 50 mg q4w	MTX 20 mg/w	5 mg daily	GOL 100 mg q4w	MTX 20 mg/w	5 mg daily	GOL 100 mg q4w	MMF 2 g daily	5 mg daily
***Switch* 8**	ADA 40 mg wkly	IFX 5 mg/kg q6w	MTX 20 mg/w	7,5 mg daily	IFX 10 mg/kg q6w	MTX 20 mg/w	7,5 mg daily	IFX 10 mg/kg q6w	MTX 20 mg/w	7,5 mg daily
***Switch* 9**	ADA 40 mg q2w	IFX 5 mg/kg q6w	MTX 15 mg/w	12,5 mg daily	IFX 6 mg/kg q6w	MTX 15 mg/w	10 mg daily	IFX 6 mg/kg q6w	MTX 15 mg/w	7,5 mg daily
***Switch* 10**	ADA 40 mg wkly	IFX 5 mg/kg q6w	SIR 2 mg daily	25 mg daily	IFX 7 mg/kg q6w	SIR 2 mg daily	15 mg daily	IFX 10 mg/kg q6w	SIR 2 mg daily	15 mg daily
***Switch* 11**	ETN 50 mg wkly	IFX 5 mg/kg q6w	AZA 150 mg daily	10 mg daily	-	-	-	-	-	-
***Swap* 1**	IFX 12 mg/kg q6w	TCZ 162 mg wkly	MTX 20 mg/w	25 mg daily	TCZ 162 mg wkly	MTX 20 mg/w	5 mg daily	TCZ 162 mg wkly	MTX 20 mg/w	5 mg daily
***Swap* 2**	IFX 10 mg/kg q6w	TCZ 8 mg/kg q4w	AZA 150 mg daily	10 mg daily	TCZ 8 mg/kg q4w	AZA 150 mg daily	10 mg daily	TCZ 8 mg/kg q4w	AZA 150 mg daily	10 mg daily
***Swap* 3**	IFX 5 mg/kg q8w	TCZ 8 mg/kg q4w	MTX 20 mg/w	5 mg daily	TCZ 162 mg wkly	MTX 15 mg/w	5 mg daily	TCZ 162 mg wkly	MTX 15 mg/w	1,25 mg daily
***Swap* 4**	IFX 10 mg/kg q6w	TCZ 8 mg/kg q4w	MTX 20 mg/w	10 mg daily	-	-	-	-	-	-
***Swap* 5**	IFX 10 mg/kg q6w	TCZ 8 mg/kg q4w	AZA 150 mg daily	10 mg daily	-	-	-	-	-	-
***Swap* 6**	IFX 5 mg/kg q8w	TCZ 8 mg/kg q4w	MTX 15 mg/w	20 mg daily	TCZ 8 mg/kg q4w	MTX 15 mg/w	15 mg daily	-	-	-
***Swap* 7**	GOL 50 mg q4w	TCZ 8 mg/kg q4w	-	15 mg daily	TCZ 162 mg wkly	-	12,5 mg daily	TCZ 162 mg wkly	-	12,5 mg daily
***Swap* 8**	GOL 50 mg q4w	TCZ 8 mg/kg q4w	MTX 20 mg/w	-	TCZ 8 mg/kg q4w	AZA 100 mg daily	-	TCZ 8 mg/kg q4w	AZA 100 mg daily	-
***Swap* 9**	ADA 40 mg q2w	TCZ 8 mg/kg q4w	SSZ 2 g daily	5 mg daily	TCZ 8 mg/kg q4w	SSZ 2 g daily	5 mg daily	TCZ 8 mg/kg q4w	SSZ 2 g daily	7,5 mg daily
***Swap* 10**	ADA 40 mg q2w	TCZ 162 mg wkly	-	50 mg daily	TCZ 162 mg wkly	-	5 mg daily	TCZ 162 mg wkly	-	-
***Swap* 11**	ADA 40 mg q2w	TCZ 8 mg/kg q4w	MTX 15 mg/w	40 mg daily	TCZ 8 mg/kg q4w	MTX 15 mg/w	7,5 mg daily	-	-	-
***Swap* 12**	ADA 40 mg q2w	USK 45 mg q12w	-	25 mg daily	-	-	-	-	-	-

ADA: adalimumab; AZA: azathioprine; bDMARD: biologic disease modifying anti-rheumatic drug; csDMARD: conventional synthetic disease modifying anti-rheumatic drug; CYC: cyclosporine; ETN: etanercept; GOL: golimumab; IFX: infliximab; MTX: methotrexate; MMF: mycophenolate mofetil; SIR: sirolimus; SSZ: salazopyrin; TCZ: tocilizumab; USK: ustekinumab.

1a). These findings were confirmed after stratification of both groups according to the reason for first TNFi discontinuation (data not shown). In only one patient, the second bDMARD (namely, infliximab) was stopped after an allergic reaction during the drug infusion. In all the other cases, it was suspended due to inadequate disease control.

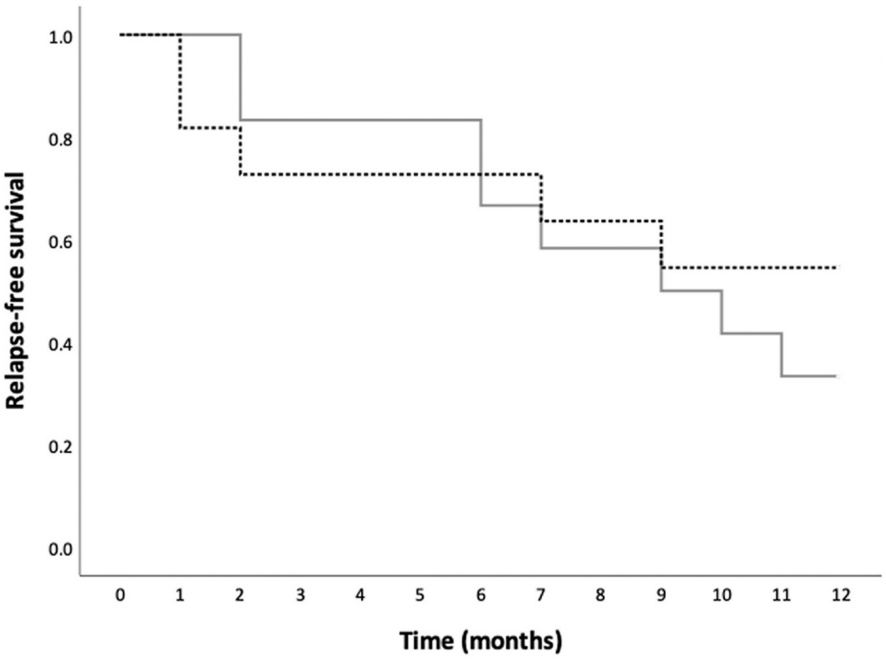
In the first 6 months after the second biologic drug start, 4 patients (36%) in the switch group and 4 patients (33%) in the swap group experienced a relapse of TAK. After extending the period of observation to the first 12 months, the numbers increased to 5 (45%) and 8 (67%) patients, respectively. Relapse free survival was equivalent between the two groups at both time points (Fig. 1b). In one patient from each of the two groups a vascular intervention was required. More precisely, one *switch* patient underwent a percutaneous transluminal angioplasty of the abdominal aorta after 5 months from the start of the second bDMARD, whereas one *swap* patient required an aorto-bifemoral bypass after 3 months.

Immunosuppressive therapy

Table II summarises dosages of second bDMARD, concomitant csDMARD, and systemic glucocorticoids at baseline, at 6 months and at 12 months.

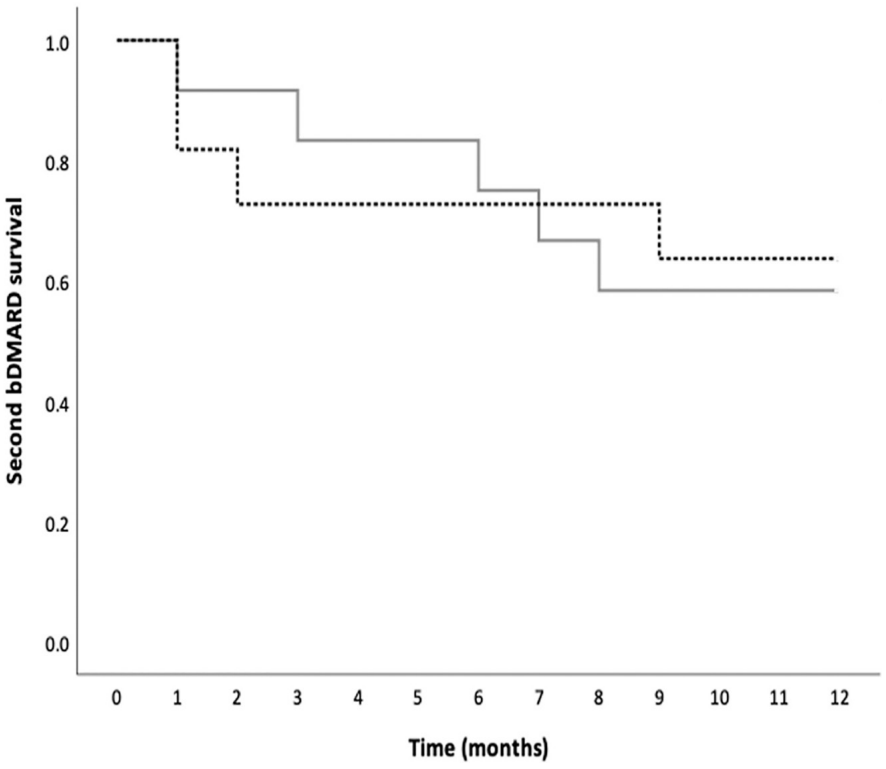
In the *swap* group, among the nine patients initially started on intravenous tocilizumab, the administration of the drug was changed to the subcutaneous route in two cases. Interestingly, 5 of the 7 *switch* patients (71%) who retained the second TNFi at 12 months, required the drug dosage to be increased (*e.g.* incrementing the dose or reducing the interval between two administrations).

In all the patients included, dosage of glucocorticoids was reduced after second bDMARD start, with the only exception of one patient from the *swap* group who needed glucocorticoid therapy to be increased. In one *swap* patient, second bDMARD start eventually allowed to suspend glucocorticoids. In one patient from the *switch* group, dosage of csDMARD therapy was reduced (namely, methotrexate from 20 mg to 15 mg weekly). In one patient from the



N. at risk													
Switch:	11	9	8	8	8	8	8	7	7	6	6	6	6
Swap:	12	12	10	10	10	10	8	7	7	6	5	4	4

Fig. 1a. Relapse-free survival at 12 months in switch (dotted line) and swap (grey line) patients. Relapse free survival at 12 months: HR = 1.45, 95% CI 0.47 – 4.45, p=0.51.



N. at risk													
Switch:	11	9	8	8	8	8	8	8	8	7	7	7	7
Swap:	12	11	11	10	10	10	9	8	7	7	7	7	7

Fig. 1b. Drug survival at 12 months in switch (dotted line) and swap (grey line) patients. Drug survival at 12 months: HR = 1.12, 95% CI 0.3 – 4.19, p=0.87.

swap group, csDMARD was changed (from methotrexate to mycophenolate mofetil) due to subjective intolerance. In all the other cases, csDMARD therapy was not modified.

Imaging assessment

At second biologic drug introduction, MRA was available for 21 patients (91%). MRA was judged as worsened compared to the last one performed before bDMARD change in 11 (52%) patients: 7 (33%) in the switch and 4 (19%) in the swap group. In the 12 months following the second biologic drug introduction, 18 (78%) patients underwent an MRA, 10 switch (56%) and 8 (44%) swap patients. MRA worsening was observed in 4 (40%) *switch* compared to 2 (25%) *swap* patients (p=0.64)

Safety

In no patient an infection event requiring hospital admission was reported. No patient had myocardial infarction or ischaemic stroke. In no patient a new diagnosis of cancer was made.

Discussion

In this study, we evaluated for the first time the efficacy and safety of bDMARDs in TAK patients refractory to first TNFi therapy. We compared whether a *switch* strategy (*i.e.* use of a different TNFi) or a *swap* strategy (*i.e.* use a bDMARD with a different mechanism of action) could be more effective in this setting of patients. Our retrospective analysis showed no differences between the two approaches at 12 months, since the number of relapses, percentage of second bDMARD failure, second bDMARD survival rate, MRA worsening, and percentage of patients undergoing vascular intervention were all comparable between the two groups.

It is worth noticing that the overall rate of failure at 12 months was high in both groups, as more than one-third of patients experienced a failure also with the second bDMARD, thus suggesting that the refractoriness to a first TNFi treatment is itself a negative prognostic factor for the efficacy of a second biologic drug, as already observed in other rheumatic conditions (17). Interestingly, we also found that in the majority of *switch* patients who retained the second TNFi throughout the 12-month follow-up, it was necessary to progressively increase TNFi doses, further supporting the hypothesis of an intrinsic more difficult-to-treat disease phenotype. Moreover, even with the limited number of imaging studies we could retrospectively evaluate, a significant vascular worsening was observed in both groups. Of note, no safety issue emerged in our analysis with the two therapeutic approaches, suggesting that both could be safely pursued in TAK patients failing first-line TNFi.

Although the role of biologic agents, especially TNFi and tocilizumab, has already been investigated both in relapsing and refractory TAK (18-21), and their use has been included in the 2018 EULAR recommendations for the management of large-vessel vasculitis (8), no previous study has specifically evaluated the outcomes of TAK patients treated with a second bDMARD. That is why the EULAR recommendations advise to consult an expert centre in case of first bDMARD failure (8). Similarly to rheumatoid arthritis, where TNFi are frequently the first class of bDMARD introduced, the majority of TAK patients are currently treated in first-line with a TNFi (22). Nonetheless, up to 23% of TAK patients treated with a first-line TNFi can be refractory to this treatment and might need the introduction of a second bDMARD (11). While different bDMARD strategies have been used with various degrees of success in refractory TAK patients (23-26), tocilizumab and TNFis still represent the drugs with the highest published and more extensive real-life experiences (27). That is why, upon TNFi failure, the clinical question is whether to switch the patient to a different TNFi or to modify the biologic therapy with the introduction of bDMARD with a different mechanism of action, mainly tocilizumab. Given the absence of significant differences, our retrospective study suggests that in this context both *switch* and *swap* strategies can be considered as suitable approaches.

Our study has some limitations. First, the retrospective nature and the small number of patients included limit the strength of our findings. Clearly this is due to the rarity of the disease. Another limitation is the absence of a precise imaging evaluation, as only a fraction of patients underwent MRA and the timing of the follow-up imaging re-evaluations were different among patients. Nonetheless, as patients were all managed in referral centres with expertise in the treatment of TAK patients, and patients included were all followed up for at least 12 months after the second bDMARD introduction, our study offers a first insight on the outcome of this population of TAK patients.

Further prospective studies with a higher number of patients are though required to confirm our findings. Moreover, as the potential arsenal of biologic drugs for refractory TAK patients has recently been enriched by the introduction of a second anti-IL6 drug (sarilumab) and JAK-inhibitors (28), we do not know whether our findings will be confirmed in other populations, such as TNFi refractory TAK patients swapping to other classes of bDMARD or TAK patients refractory to tocilizumab first-line therapy either switched to sarilumab or swapped to other bDMARDs.

Take home messages

- No data are available on which strategy (*switch* or *swap*) is more effective in refractory TAK patients failing first-line TNFi therapy.
- We compared the 12-month efficacy and safety of a second bDMARD in TAK patients switched to a different TNFi or swapped to a bDMARD with a different mechanism of action.
- We observed that in first-line TNFi failure TAK patients both *switch* and *swap* strategies can be considered suitable approaches.

Competing interests

C. Campochiaro reports personal fees from Roche and SOBI, outside the submitted work.

E. Baldissera reports Speaker's Bureau fees from Roche and Pfizer.

A. Ravelli reports grant support and/or speaking and consultant fees from AbbVie, Angelini, Bristol-Myers-Squibb, Novartis, Pfizer, Reckitt-Benkiser,

Roche and Johson & Johnson outside the submitted work.

C. Salvarani reports consulting fees from AbbVie, Lilly, Pfizer and Roche outside the submitted work.

L. Dagna has served as consultant for Celltrion, Roche, Sanofi, AbbVie and Amgen outside the present work.

The other co-authors have declared no competing interests.

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