Persistence of remission after lengthening of golimumab in inflammatory joint diseases

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Abstract

Objective

In refractory inflammatory joint diseases (IJDs) biological disease-modifying anti-rheumatic drugs (bDMARDs) may achieve remission. EULAR recommends bDMARD tapering when remission persists. However, guidelines on tapering modalities and criteria for patient selection are lacking. We aimed to evaluate remission persistency after lengthening the time between injections of golimumab in patients affected by IJD and to identify any patient or disease characteristics associated to flare after lengthening.

Methods

Patients affected by rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and juvenile idiopathic arthritis (JIA) treated with golimumab were enrolled in a retrospective observational study. Demographic data, ESR, cRP, DAS28/ BASDAI, were collected at baseline and during the follow-up (T1- defined as a medical check-up after 1 year of treatment or, for patients with longerg exposure, the first medical check-up in 2016, when at our unit we began to experience drug tapering- and T2- 12 months after the lengthening was started). In 22/80 patients in remission at T1, injection time was lengthened.

Results

Eighty patients were enrolled, 34 AS, 33 PsA, 9RA and 4 JIA. At baseline, all had an active disease. At T1, 60/80 patients reached remission and 22/60 patients started tapering. At T2, 20/22 pts (91%) were in remission. At T1 BASDAI was higher (2.2, SD 0.28 vs. 0.58, SD 0.47; p<0.001) in patients who lost remission at T2. Patients who flared recovered remission once taken back to a 28-day interval. 4/38 patients maintained at the standard dose flared up and switched/swapped bDMARD. The difference in retention rate toward patients on reduced dose was not significant.

Conclusion

Results show that golimumab lengthening is safe and successfully maintains remission. In patients who experienced a flare after lengthening, the standard regimen promptly restored remission.

Key words

inflammatory joint diseases, anti-TNF-alpha inhibitors, golimumab, tapering, lengthening

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Introduction

Inflammatory joint diseases (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis) are characterised by pain and progressive structural damage determining disability and worsening of life quality. Advances in the knowledge about the pathogenesis of these clinical conditions has allowed the identification of tumour necrosis factor alpha (TNF-α) as one of the leading cytokines, involved in their pathogenetic pathway. This led to the development of biotechnological drugs, targeting TNF-alpha cascade and blocking the inflammatory process with important therapeutic results.

Five different TNF-α inhibitors have been approved for the treatment of IJD: infliximab, etanercept, adalimumab, golimumab, and certolizumab-pegol.

These drugs are able not only to control clinical symptoms, but also to reduce or even stop the evolution of anatomical damage derived from inflammation. They are therefore able to act as "disease modifiers" even in patients refractory to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate, hydroxychloroquine, etc. (1, 2).

Golimumab (SIMPONI®) is a fully human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology which, binding the soluble human TNF-alpha and the active transmembrane TNF-alpha, prevents its link to specific receptors. In rheumatology, it is approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and juvenile idiopathic arthritis (JIA).

After a single subcutaneous administration, golimumab reaches maximum serum concentrations between day 2 to 6. Repeated dosing every 4 weeks (every 28 days) leads to steady state plasma levels from week 12. The half-life value was estimated to be approximately 12±3 days in healthy subjects (3).

According to the latest EULAR recommendations for the management of inflammatory joint diseases (4-6), when remission persists, tapering of biological DMARD (bDMARDs) may be considered. However, the notion of "persistent remission" is still not clearly defined and indications on tapering modality are still lacking. Moreover, in the literature, "tapering" generically refers to the reduction of the total amount of DMARD given to a patient. It can be performed in two distinct ways: lengthening (spacing) the interval between intravenous (iv) or subcutaneous (sc) administrations or reducing the drug dosage maintaining the same therapeutic interval (13). For practical reasons, the lengthening strategy is more common, particularly with sc bDMARDs, while dose reduction is reserved in some cases for iv bDMARDs. In fact, lengthening also allows the reduction of drug burden either in young patients without comorbidity or in older patients with polypharmacotherapy, thus improving quality of life (14, 15, 16, 19, 22-27, 29, 30).

The aim of our study was to evaluate the persistency of remission after increasing the interval between injections of golimumab in patients affected by RA, PsA, AS and JIA and to identify any variables associated to disease flare after lengthening.

Patients, material and methods

From January 2011 to July 2020, 80 patients affected by RA, AS, PsA and JIA treated with Golimumab (monotherapy or in combination with csDMARDs) and followed up at the Rheumatology of the AOU Careggi in Florence, satisfying the inclusion criteria (age >18 years, signature of the informed consent, prednisone or equivalent at the maximum dose of 5 mg/die) were enrolled.

A retrospective observational study was performed. Analysed variables were demographical data, diagnosis, disease duration, associated csDMARDs (Methotrexate, Hydroxychloroquine, Sulfasalazine and Leflunomide), corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs), extra- articular manifestations related to rheumatological disease (IBD, skin psoriasis, uveitis), duration of standard dose therapy (50 mg sc every 28 days) and days between doses after lengthening. The positivity of Rheumatoid Factor, anti-CCP antibodies and HLA B27 was also

assessed. At baseline (T0) inflammation (ESR and cRP), clinimetric indices for the evaluation of disease activity were evaluated. Specifically, DAS28 (Disease Activity Score 28) was used for RA, PsA with peripheral involvement and JIA, BASDAI (Bath AS Disease Activity Index) for AS and PsA with axial involvement. According to EULAR (European League Against Rheumatism), a DAS28 value <2.6 defined clinical remission, as well as a BASDAI< 4. Same variables were analysed at T1, defined as a medical check-up after 1 years of treatment (or, for patients with longer golimumab exposure, the first medical check-up in 2016, when at our unit we began to experience drug tapering).

In 22/60 patients in clinical remission at T1, after a shared decision between patient and rheumatologist, the time between golimumab injections was prolonged of 3 days every 3 months. The following variables were evaluated 12 months after the lengthening was started (T2): ESR, cRP, DAS28, BASDAI, time between Golimumab injections (measured in days).

Statistical analysis was performed using software R 3.5.2 GUI 1.70 El Capitan build (7612). For the descriptive statistics part, continuous variables, after verifying their normality with Kolmogorov-Smirnov and Shapiro-Wilk tests, were represented by indicating the average and standard deviation; continuous variables not normally distributed were expressed by median and interquartile ranges; categorical variables were described by frequency distribution. A multivariate analysis was carried out, tested by Fisher's exact test for dichotomous variables and the Chi-squared test for categorical variables with more than one level. A logistic regression analysis was also performed considering as outcome variable the presence of remission at T1 and as predictors the variables concerning characteristics of patients at T0 as well as inflammation and clinimetric indices at T0. Finally, a logistic regression analysis was employed considering as outcome variable the persistence of remission at T2 and as predictors the variables concerning patient characteristics at T0 as well as inflammation and clinimetric indices at T0, T1, T2.

The study was approved by the local Ethic Committee "Comitato Etico Regionale per la Sperimentazione Clinica della Toscana - sezione AREA VASTA CENTRO" (approval no.: 18607_oss).

Table I. Patients' baseline characteristics.

n		80
Age (SD)		50.62 (13.91)
Sex (%)	M	32 (40.0)
Disease duration, years (SD)		11.45 (6.70)
Disease (%)	RA	8 (10.0)
	AS	33 (41.2)
	PsA	32 (40.0)
	Other	7 (8.8)
B27 (%)	No	58 (72.5)
	Yes	22 (27.5)
B35 (%)	No	72 (90.0)
	Yes	8 (10.0)
CCP (%)	No	70 (87.5)
	Yes	10 (12.5)
FR (%)	No	65 (81.2)
	Yes	15 (18.8)
Psoriasis (%)	No	58 (72.5)
	Yes	22 (27.5)
IBD (%)	No	69 (86.2)
	Yes	11 (13.8)
Uveitis (%)	No	72 (90.0)
	Yes	8 (10.0)
Treatment		
NSAIDs (%)	No	74 (92.5)
	Yes	6 (7.5)
HCQ (%)	No	71 (88.8)
	Yes	9 (11.2)
Leflunomide (%)	No	77 (96.2)
	Yes	3 (3.8)
MTX (%)	No	56 (70.0)
	Yes	24 (30.0)
Sulfasalazine (%)	No	70 (87.5)
	Yes	10 (12.5)
Steroids (%)	No	65 (81.2)
	Yes	15 (18.8)
high CRP (%)	No	34 (42.5)
	Yes	46 (57.5)
CRP (v.n. <0.5)		1.07 (1.23)
high ESR (%)	No	44 (55.0)
	Yes	36 (45.0)
ESR (v.n. <25)		21.96 (15.47)
BASDAI (SD)		4.68 (1.80)
DAS28 (SD)		4.56 (0.99)
Standard dose duration months (SD)		37.94 (22.77)

Results

From January 2011 to July 2020, 80 patients on Golimumab were enrolled (32 male and 48 female, mean age 50.6 years ± 13.91; 34 AS, 33 PsA, 9 RA and 4 JIA). The patients' characteristics are summarised in Table I. The average duration of the disease was 11.45 years (SD 6.7). The median duration in months of standard-dose Golimumab therapy between T0 and T1 was 36.50 months (inter-quartile range 17–57). Regarding the duration of the treatment, 26 patients were on therapy for less than 2 years, 25 for less than 4 years, 23 for less than 6 years and 6 from 6 to

8 years. 54% of patients (43/80) were at least one csDMARD in combination with golimumab without significant differences between diseases (p<0.14); 15 patients were on steroid therapy and 6 patients on NSAIDs. 37% of patients had at least one comorbidity: psoriasis (22 pts), chronic inflammatory bowel disease (11 pts), and uveitis (8 pts)

At baseline, the average DAS 28 was 4.74 (SD 0.85) and the average BASDAI was 5.23 (SD 1.31), showing an active disease. At T1, 75% of patients (60/80) were in remission, with an average DAS 28 of 1.84 (SD 0.6) and an average BASDAI of 1.32 (SD 0.6); 85% patients with active disease at T1 (17/20) were female (p=0.001).

Steroids were used by 18.8% of total population (of whom 98% had RA). Steroids use (at a mean dose of 2 mg methylprednisolone ± 0.5) was significantly less frequent (p<0.009) in patients in remission at T1: 40% of patients with active disease *versus* 11.7% of patients in remission. A longer time of standard dose therapy of golimumab was observed in patients in remission at T1 (p<0.05).

At T1, patients in remission were proposed to start lengthening the therapy: only 37% of patients (22/60) in remission agreed to extend the interval between injections (3 days more every 3 months). Patients who increased the intervals at T1 had a longer duration of standard-dose therapy (p=0.02) with 0% of patients (*vs*. 39.5% of the remission group maintaining the full dose) in therapy for less than 2 years. Tapering was started after a median of 35.89 months of standard dose therapy. In patients who increased the intervals, a significantly lower frequency of association with methotrexate (42% *vs*. 13.6%, p=0.025) was also observed. Furthermore, patients in remission who prolonged the therapeutic interval had a lower average BASDAI at T1 (0.78, SD 0.71) compared to those who did not taper (1.61, ss 1.11) (p=0.01), (Table II). At T2, 91% (20/22) of patients who increased the intervals, were still in remission, with an average DAS 28 1.9 (SD 0.49) and an average BASDAI of 0.8 (SD 0, 67). The average therapeutic interval for patients who maintained remission at T2 after lengthening was 43 days (ds 3 days). At T1, a significantly higher BASDAI, (2.2, SD 0.28 *vs*. 0.58, SD 0.47; p<0.001) was observed in patients who, after extending the therapeutic interval, were no longer in remission at T2 (Table III). During the T2 assessment, 3 patients discontinued therapy due to persistence of remission, while 2 patients with a flare went back to the standard interval achieving again disease remission. Among 38 patients who maintained the standard interval of administration, 4 experienced a disease flare with a switch or swap to bDMARD. In this group the retention rate was 90%. The difference of retention rate between patients on standard interval *vs* those on lengthening was not statistically significant.

Regression analysis revealed male sex as a possible positive predictor of remission at T1 (OR 41.1 IC 2.26–748, p=0.01), and disease duration expressed in years as a negative predictor (OR 0.763, IC 0.626–0.929, p=0.007). From regression analysis. regarding remission at T2, no predictor resulted signifi-

Table II. Comparison between reducers and non-reducers at T1.

		REDUCTION T1		
		No	Yes	p-value
n		38	22	
Age (SD)				
Sex (%)	M	19 (50.0)	11 (50.0)	0.1
Disease duration, years (SD)		10.87 (7.69)	11.09 (4.99)	0.9
Disease (%)	RA	4 (10.5)	2 (9.1)	0.4
	AS	20 (52.6)	7 (31.8)	
	PsA	13 (34.2)	12 (54.5)	
	Other	1 (2.6)	1 (4.5)	
B27 (%)	No	27 (71.1)	15 (68.2)	0.1
	Yes	11 (28.9)	7 (31.8)	
B35 (%)	No	33 (86.8)	21 (95.5)	0.4
	Yes	5 (13.2)	1 (4.5)	
CCP (%)	No	33 (86.8)	20 (90.9)	0.1
	Yes	5 (13.2)	2 (9.1)	
FR (%)	No	32 (84.2)	18 (81.8)	0.1
	Yes	6 (15.8)	4 (18.2)	
Psoriasis (%)	No	25 (65.8)	16 (72.7)	0.8
	Yes	13 (34.2)	6 (27.3)	
IBD (%)	No	31 (81.6)	21 (95.5)	0.3
	Yes	7 (18.4)	1 (4.5)	
Uveitis (%)	No	35 (92.1)	20 (90.9)	0.1
	Yes	3 (7.9)	2 (9.1)	
Treatment				
NSAIDs (%)	No	35 (92.1)	21 (95.5)	0.1
	Yes	3 (7.9)	1 (4.5)	
HCQ (%)	No	36 (94.7)	21 (95.5)	0.1
	Yes	2 (5.3)	1 (4.5)	
Leflunomide (%)	No	37 (97.4)	20 (90.9)	0.4
	Yes	1 (2.6)	2 (9.1)	
MTX (%)	No	22 (57.9)	19 (86.4)	**0.025**
	Yes	16 (42.1)	3 (13.6)	
Sulfasalazine (%)	No	34 (89.5)	20 (90.9)	0.1
	Yes	4 (10.5)	2 (9.1)	
Steroids (%)	No	32 (84.2)	21 (95.5)	0.2
	Yes	6 (15.8)	1 (4.5)	
BASDAI T0		5.36 (1.65)	4.80 (0.62)	0.2
BASDAI T1		1.61 (1.11)	0.78 (0.71)	**0.01**
DAS28 T0		4.72 (0.97)	5.03 (0.47)	0.3
DAS28 T1		1.77 (0.65)	1.93 (0.52)	0.4
Standard dose duration months (SD)		35.89 (22.45)	49.23 (17.27)	**0.02**

Table III. Comparison between patients with and without sustained remission after tapering.

		REMISSION T2		
		No	Yes	*p*-value
n		2	20	
Age (SD)		49.00 (0.00)	51.75 (14.79)	0.8
Sex (%)	M	0 (0.0)	11 (55.0)	0.5
Disease duration, years (SD)		5.50 (2.12)	11.65 (4.87)	0.9
Disease (%)	RA	0 (0.0)	2 (10.0)	0.6
	AS	0 (0.0)	7 (35.0)	
	PsA	2 (100.0)	10 (50.0)	
	Other	0 (0.0)	1 (5.0)	
B27 (%)	No	1 (50.0)	14 (70.0)	0.1
	Yes	1 (50.0)	6 (30.0)	
B35 (%)	No	2 (100.0)	19 (95.0)	0.1
	Yes	0 (0.0)	1 (5.0)	
CCP (%)	No	2 (100.0)	18 (90.0)	0.1
	Yes	0 (0.0)	2 (10.0)	
FR (%)	No	1 (50.0)	17 (85.0)	0.3
	Yes	1 (50.0)	3 (15.0)	
Psoriasis (%)	No	1 (50.0)	15 (75.0)	0.5
	Yes	1 (50.0)	5 (25.0)	
IBD (%)	No	2 (100.0)	19 (95.0)	0.1
	Yes	0 (0.0)	1 (5.0)	
Uveitis (%)	No	2 (100.0)	18 (90.0)	0.1
	Yes	0 (0.0)	2 (10.0)	
Treatment				
NSAIDs (%)	No	2 (100.0)	19 (95.0)	0.1
	Yes	0 (0.0)	1 (5.0)	
HCQ (%)	No	2 (100.0)	19 (95.0)	0.1
	Yes	0 (0.0)	1 (5.0)	
Leflunomide (%)	No	2 (100.0)	18 (90.0)	0.1
	Yes	0 (0.0)	2 (10.0)	
MTX (%)	No	2 (100.0)	17 (85.0)	0.1
	Yes	0 (0.0)	3 (15.0)	
Sulfasalazine (%)	No	2 (100.0)	18 (90.0)	0.1
	Yes	0 (0.0)	2 (10.0)	
Steroids (%)	No	2 (100.0)	19 (95.0)	0.1
	Yes	0 (0.0)	1 (5.0)	
high CRP T0 (%)	No	1 (50.0)	6 (30.0)	0.1
	Yes	1 (50.0)	14 (70.0)	
high CRP T1 (%)	No	2 (100.0)	19 (100.0)	NA
	Yes	0 (0.0)	0 (0.0)	
high CRP T2 (%)	No	2 (100.0)	19 (95.0)	0.1
	Yes	0 (0.0)	1 (5.0)	
high ESR T0 (%)	No	0 (0.0)	8 (40.0)	0.5
	Yes	2 (100.0)	12 (60.0)	
high ESR T1 (%)	No	2 (100.0)	16 (80.0)	0.1
	Yes	0 (0.0)	4 (20.0)	
high ESR T2 (%)	No	1 (50.0)	15 (75.0)	0.5
	Yes	1 (50.0)	5 (25.0)	
BASDAI T0		5.50 (0.28)	4.39 (1.66)	0.8
BASDAI T1		2.20 (0.28)	0.66 (0.63)	**0.03**
BASDAI T2		4.05 (0.07)	0.96 (0.77)	**<0.001**
DAS28 T0		5.45 (0.49)	4.80 (0.71)	0.2
DAS28 T1		2.50 (0.57)	1.92 (0.59)	0.2
DAS28 T2		3.35 (0.21)	2.03 (0.56)	**0.04**
Standard dose duration months (SD)		47.50 (24.75)	49.40 (17.23)	886

cant. In patients who increased the interval between injections, linear regression analysis showed a positive correlation between the BASDAI values at T1 and BASDAI values at T2 (correlation coefficient 1.14, $p<0.0001$).

Discussion

Our results confirm the previous literature showing the efficacy of golimumab in patients suffering from inflammatory joint diseases (7-10). In fact, in 75% of enrolled patients disease remission was observed.

In our study we observed a longer duration of standard-dose therapy in patients in remission than in those who did not reach remission at T1 ($p=0.05$). In agreement with the literature, our regression analysis showed a significant higher probability of achieving remission in patients with a shorter disease duration (OR 0.763, CI 0.626–0.929, $p=0.007$) (11, 12).

As low disease activity or remission are achieved in patients suffering from rheumatic diseases, the possibility to taper or withdraw bDMARDs is now gaining attention in order to reduce drug-related adverse events and to contain costs. In several studies and in different inflammatory joint disease, tapering of bDMARDs has been assessed providing evidence of retained efficacy and, in case of flare, a prompt control of disease after reintroduction of standard dose therapy. Park *et al*. and Verhoef *et al*. (15, 16) suggested that a gradual reduction of anti-TNF alpha has an efficacy comparable to standard dose maintenance in patients suffering from AS and RA, respectively, and in remission. This result has been also observed in our patients where 91% of those who extended the standard interval remained in remission.

However, still several questions wait for an answer. In fact, it is still debated what should be the characteristics of patients eligible and the modalities for starting a drug tapering or lengthening process. In the SLR on the efficacy of pharmacological treatment in RA (18), Kerschbaumer *et al*. analysed 9 tapering studies. These revealed that dose reduction of bDMARDs is feasible, and that risk of flare is lower when

dose reduction is started after sustained stringent remission instead of tapering just in sustained low disease activity.

So far, EULAR recommendations 4–6 do not clearly identify how long remission should last before reducing the bDMARD dose, even if six months of persistent remission is indicated as a reasonable time. Moreover, the concept of remission itself is not uniquely defined. Different remission criteria are use through different studies, DAS28-CRP being the most employed, along with EULAR/ACR remission criteria (17).

Sometimes tapering is started even in patient presenting low disease activity (19) although this practice accounts for a higher risk of flares.

For all these reasons, in our study, the choice between starting lengthening or continuing standard dose treatment was made after a shared decision among the rheumatologist and patients in remission according to DAS 28 PCR score for patients with peripheral arthritis and to BASDAI score in those with predominance of axial involvement.

Our data indicate that the duration of standard dose therapy in patients lengthening the standard interval between doses, was significantly higher (p=0.02) than in patients who kept the standard therapeutic range and tapering was not started in patients treated at standard dose for less than 2 years. Moreover, subjects in remission with axial involvement that increased the length of administration, had a significantly lower BASDAI than those who did not lengthen, (average BASDAI 0.78±0.71 *vs*. 1.61±1.11, p=0.01). It could be hypothesised that a longer period of previous treatment and a low disease activity may have favoured the decision of the patients to share the medical choice to start lengthening. In patients that increased the treatment interval, a significantly lower frequency of association with methotrexate (42% *vs*. 13.6%, p=0.025) was also observed.

Other studies were performed starting tapering after a shared decision between patients and rheumatologist. In the HONOR study (20), 52/75 RA patient in remission chose to taper adalimumab. In line with our findings, they had lower dose of concomitant MTX when compared to those maintaining standard therapy.

Evidence is scarce in terms of differences between firstly tapering bDMARDs/tsDMARDs or csDMARDs (25), so that EULAR recommendations invite to choose the first strategy. But it is a common experience that patients in combination therapy with bDMARDs and csDMARDs often become intolerant to csMDARDs, leading to their withdrawal in patients in remission.

Fong *et al*. (22) analysed the outcome of tapering in a cohort of 125 AS and 83 PsA patients treated with anti-TNF alpha: 35% of eligible patients agreed to reduce anti-TNF alpha dosage. In this case, older male AS patients with longer disease duration and currently on their first biologic were more likely to agree to undertake dose reduction of anti-TNF alpha therapy.

To standardise tapering strategy and to reduce the risk of flare, it would be important to identify what clinical, biological, and radiological features are associated to the lower risk of relapse after tapering.

In our group, we observed a significantly higher BASDAI at T1 (p<0.001), in patients who, after lengthening were no longer in remission at the last check-up (2.2 *vs*. 0.58). Moreover, linear regression analysis evidenced a positive correlation, between the BASDAI values at T1 and those at T2. This could suggest the utility to identify a cut-off value of disease activity index within the range of inactive disease, below which there is a higher probability of remission persistence.

In our study, duration of standard dose therapy and disease duration did not differ significantly between patients with persistent remission at T2 and patients who instead underwent a flare. Likewise, the presence of psoriasis, uveitis, IBD, the positivity of CCP and RF and the B27 status did not modify the risk of relapse.

The lack of significant difference in terms of presence of extra-articular manifestations could be due to the small sample number and also to the small number (10%) of patients who experienced a disease flare.

In 2016, Schett and colleagues reviewed 28 studies evaluating tapering/withdrawal of different bDMARDs in patients affected by RA (19). As risk factors for flares, most of the studies recognised longer disease duration and higher DAS28 at the time of starting tapering. Data from Naredo *et al*. (23), Iwamoto *et al*. (24) and Alivernini *et al*. (25) highlighted the possible role of US in predicting flares as they often found subclinical synovitis in patients who relapsed after tapering.

Vittecoq *et al*. (26) recently analysed the factors associated to relapse in a cohort of 53 RA patients treated with anti-TNF alpha, abatacept or tocilizumab, who tapered and then discontinued their bDMARDs. After 18 months of follow-up, 12 maintained bDMARD-free remission, 39 relapsed and 2 were lost at follow-up. In multivariate analysis, baseline factors predictive of relapse were longer disease duration, no methotrexate intake, corticosteroid intake and female gender. They also performed a survival analysis, where the main risk factor of relapse after discontinuation was an increase of SDAI >0 during the spacing period (p=0.03). In this case, US findings were not able to predict flares.

The PREDICTRA study (27) investigated the association between residual baseline disease activity detected by MRI and the occurrence of flares in patients with RA in persistent long-standing clinical remission randomised to a tapering strategy or adalimumab withdrawal. As a result, baseline MRI inflammation was not associated with flares, neither any patients baseline characteristics.

The literature on anti-TNF alpha tapering was reviewed for AS patients by Navarro-Compàn and colleagues (28), including 8 studies on dose reduction and 5 on discontinuation. The authors stated that, overall, published data are scarce and the level of evidence of the studies is weak. What emerged is that tapering is a feasible option for AS patients with high rate of remission maintenance, while complete bDMARD withdrawal is often associated with disease flares. In this analysis, time under remission before tapering anti-TNF therapy as well as the absence

of peripheral and extra-articular manifestations are associated with a better outcome.

Fong *et al*. (21) found that in AS patients, baseline disease in patients who successfully reduced their dose of anti-TNF alpha did not differ from the one of patients with failures of anti-TNF alpha dose reduction (mean BASDAI 2.0±1.5 *vs*. .2.8±1.2, respectively, p=0.128). According to Carron *et al*., (29) after the withdrawal of golimumab in a cohort of patients with peripheral AS, disease flares were associated to the presence of cutaneous psoriasis and to a polyarticular disease (SJC ≥5), while the presence of B27 seemed to be protective.

Lorenzin *et al*. (30) studied for the first time the lengthening of the treatment with etanercept and adalimumab in psoriatic arthritis: the interval between injections was extended in 46.1% of the patients (35% for adalimumab 58% for etanercept) and the patients did not experience any disease relapse. Thus, the results indicated that the interval therapy interval which could be reached was 3.12 weeks for adalimumab (with respect to 2 weeks) and 2.75 weeks for etanercept (with respect to 0.5 weeks). This result is in line with our data and suggests that lengthening can be safe and maintain the remission also in PsA. Data on PsA patients from the study by Fong *et al*. (21) showed that remission was more likely in those with lower disease activity prior to anti-TNF alpha dose reduction (mean DAS28-ESR 1.1±0.5 *vs* .2.1±0.9, p=0.021), thus confirming our findings on the importance of starting lengthening only when remission is deep and stable.

Limitations of this study include the small sample number, the non-homogeneity of the examined diseases, and the observational and retrospective nature. Moreover, the absence of guidelines on tapering does not allow a consistent comparation between works present in the literature.

Conclusions

Our data confirm the efficacy of Golimumab in controlling inflammatory joint disease and in the maintenance of remission. Moreover, its efficacy is maintained also during lengthening with a retention of remission in 91% of patients. Drug lengthening reduced the risk of side effects and the number of visits to the hospital, thus containing the costs for the Health system. Starting lengthening once stringent and persistent remission is achieved seems to reduce the probability of flares. Further studies on larger populations are needed to identify any other predictors associated to a lower risk of disease reactivation after lengthening.

References

1. LIPSKY PE, VAN DER HEIJDE DM, ST CLAIR EW *et al*.: Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group: infliximab and methotrexate in the treatment of rheumatoid arthritis. anti.tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy Study Group. *N Engl J Med* 2000; 343(22): 1594-602. https://doi.org/10.1056/nejm200011303432202
2. MEASE PJ, KIVITZ AJ, BURCH FX *et al*.: Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum*. 2004; 50(7): 2264-72. https://doi.org/10.1002/art.20335
3. European Medicines Agency (EMA). European Assessment Report (EPAR) for golimumab. Procedure No EMEA/H/C 0009992. Avaiable from http//www.ema.europa.eu
4. VAN DER HEIJDE D, RAMIRO S, LANDEWÉ R *et al*.: 2016 update of the ASAS-EULAR management recommendations for axial spondylarthritis. *Ann Rheum Dis*. 2017; 76(6): 978-91. https://doi.org/10.1136/annrheumdis-2016-210770
5. COATES LC, GOSSEC L, RAMIRO S *et al*.: New GRAPPA and EULAR recommendations for the management of psoriatic arthritis. *Rheumatology* 2017; 56(8): 1251-3. https://doi.org/10.1093/rheumatology/kew390
6. SMOLEN JS, LANDEWÉ RBM, BIJLSMA JWJ *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; 79(6): 685-99. https://doi.org/10.1136/annrheumdis-2019-216655
7. KEYSTONE E, GENOVESE MC, KLARESKOG L *et al*.: Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Ann Rheum Dis* 2010; 69(6): 1129-35. https://doi.org/10.1136/ard.2009.116319
8. SMOLEN JS, KAY J, DOYLE MK *et al*.: Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alpha inhibitors (GO-AFETR study): a multicentric, randomized, double-blind, placebo controlled, phase III trial. *Lancet* 2009; 374(9685): 210-21. https://doi.org/10.1016/s0140-6736(09)60506-7
9. EMERY P, FLEISCHMANN RM, MORELAND LW *et al*.: Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate naïve patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009; 60(8): 2272-83. https://doi.org/10.1002/art.24638
10. KAVANAUGH A, MCINNES I, MEASE P *et al*.: Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: a 24-week efficacy & safety results of randomized, placebo-controlled study. *Arthritis Rheum* 2009; 60(4): https://doi.org/10.1002/art.24403 976-86.
11. EINARSSON JT, WILLIM M, ERNESTAM S SAXNE T, GEBOREK P, KAPETANOVIC MC: Prevalence of sustained remission in rheumatoid arthritis: impact of criteria sets and disease duration, a Nationwide Study in Sweden. *Rheumatology* (Oxford) 2019; 58(2): 227-36. https://doi.org/10.1093/rheumatology/key054
12. XIE W, LI J, ZHANG X, SUN X, ZHANG Z: Sustained clinical remission of rheumatoid arthritis and its predictive factors in an unselected adult Chinese population from 2009 to 2018. *Int J Rheum Dis*. 2019; 22(9): 1670-8. https://doi.org/10.1111/1756-185x.13651
13. VERHOEF LM, TWEEHUYSEN L, HULSCHER ME *et al*.: bDMARD dose reduction in rheumatoid arthritis: a narrative review with systematic literature search. *Rheumatol Ther* 2017; 4(1): 1-24. https://doi.org/10.1007/s40744-017-0055-5
14. GONZÁLEZ-GAMBOA LM, BAROCIO-RAMÍREZ AK, ROCHA-MUÑOZ AD *et al*.: Disease Activity Score on 28 joints and polypharmacy are independent predictors for health-related quality of life evaluated by INCAVISA in patients with rheumatoid arthritis. *J Clin Rheumatol*. 2016; 22(8): 399-404. https://doi.org/10.1097/rhu.0000000000000463
15. PARK JW, KIM HA, SHIN K *et al*.: Effects of tapering tumor necrosis factor inhibitor on the achievement of inactive disease in patients with axial spondyloarthritis: a nationwide cohort study. *Arthritis Res Ther.* 2019; 21(1): 163. https://doi.org/10.1186/s13075-019-1943-6
16. VERHOEF LM, VAN DEN BEMT BJ, VAN DER MAAS A *et al*.: Down titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. *Cochrane Database Syst Rev* 2019; 5(5): CD010455. https://doi.org/10.1002/14651858.cd010455.pub3
17. KERSCHBAUMER A, SEPRIANO A, SMOLEN JS *et al*.: Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2020; 79(6): 744-59. https://doi.org/10.1136/annrheumdis-2019-216656
18. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011; 63(3): 573-86. https://doi.org/10.1002/art.30129

19. SCHETT G, EMERY P, TANAKA Y *et al*.: Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. *Ann Rheum Dis* 2016; 75(8): 1428-37. https://doi.org/10.1136/annrheumdis-2016-209201
20. TANAKA Y, HIRATA S, KUBO S *et al*.: Dis-continuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. *Ann Rheum Dis* 2015; 74(2): 389-95. https://doi.org/10.1136/annrheumdis-2013-204016
21. VAN MULLIGEN E, WEEL A, KUIJPER TM *et al*.: Gradual tapering TNF blockers versus conventional synthetic DMARDs in patients with rheumatoid arthritis in sustained remission: first year results of the randomised controlled TARA study. *Ann Rheum Dis* 2019; 78(6): 746-53. https://doi.org/10.1136/annrheumdis-2018-214970
22. FONG W, HOLROYD C, DAVIDSON B, ARMSTRONG R: The effectiveness of a real life dose reduction strategy for tumour necrosis factor inhibitors in ankylosing spondylitis and psoriatic arthritis. *Rheumatology* (Oxford) 2016; 55(10): 1837-42. https://doi.org/10.1093/rheumatology/kew269
23. NAREDO E, VALOR L, DE LA TORRE I *et al*.: Predictive value of Doppler ultrasound-detected synovitis in relation to failed tapering of biologic therapy in patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2015; 54(8): 1408-14. https://doi.org/10.1093/rheumatology/kev006
24. IWAMOTO T, IKEDA K, HOSOKAWA J *et al*.: Prediction of relapse after discontinuation of biologic agents by ultrasonographic assessment in patients with rheumatoid arthritis in clinical remission: high predictive values of total gray-scale and power Doppler scores that represent residual synovial inflammation before discontinuation. *Arthritis Care Res* (Hoboken) 2014; 66(10): 1576-81. https://doi.org/10.1002/acr.22303
25. ALIVERNINI S, PELUSO G, FEDELE AL *et al*.: Tapering and discontinuation of TNF-alpha blockers without disease relapse using ultrasonography as a tool to identify patients with rheumatoid arthritis in clinical and histological remission, *Arthritis Res Ther* 2016; 18: 39. https://doi.org/10.1186/s13075-016-0927-z
26. VITTECOQ O, DESOUCHES S, KOZYREFF M *et al*.: Relapse in rheumatoid arthritis patients undergoing dose reduction and withdrawal of biologics: are predictable factors more relevant than predictive parameters? An observational prospective real-life study. *BMJ Open* 2019; 9(12): e031467. https://doi.org/10.1136/bmjopen-2019-031467
27. EMERY P, BURMESTER GR, NAREDO E *et al*.: Adalimumab dose tapering in patients with rheumatoid arthritis who are in long-standing clinical remission: results of the phase IV PREDICTRA study. *Ann Rheum Dis* 2020; 79(8): 1023-30. https://doi.org/10.1136/annrheumdis-2020-217246
28. NAVARRO-COMPÁN V, PLASENCIA-RODRÍ-GUEZ C, DE MIGUEL E *et al*.: Anti-TNF discontinuation and tapering strategies in patients with axial spondyloarthritis: a systematic literature review. *Rheumatology* (Oxford) 2016; 55(7): 1188-94. https://doi.org/10.1093/rheumatology/kew033
29. CARRON P, VARKAS G, RENSON T *et al*.: High rate of drug-free remission after induction therapy with golimumab in early peripheral spondyloarthritis. *Arthritis Rheumatol* 2018; 70(11); 1769-77. https://doi.org/10.1002/art.40573
30. LORENZIN M, ORTOLAN A, DE HOOGE M *et al*.: Lengthening the time intervals between doses of biological agents in psoriatic arthritis patients: A single-center retrospective study. *Int J Immunopathol Pharmacol* 2015; 28(4): 479-87. https://doi.org/10.1177/ 0394632015599446