

## Understanding the Biological Significance of Anti-DFS70 Antibodies: Effect of Biologic Therapies on Their Occurrence in Inflammatory Arthritis

To the Editor:

The anti-dense fine speckled 70 (anti-DFS70) antibodies have recently become of interest because of their occurring in heterogeneous disorders including chronic inflammatory conditions, cancer, and systemic autoimmune rheumatic diseases (SARD), as well as in healthy individuals<sup>1,2,3</sup>. The frequency of anti-DFS70 antibodies in rheumatoid arthritis (RA) ranged from 0 to 2.6%<sup>4</sup>. There have been no studies examining the frequency of anti-DFS70 antibodies in spondyloarthritis (SpA) as a group, while only 1 study evaluated anti-DFS70 positivity in ankylosing spondylitis (AS)<sup>5</sup>. These autoantibodies could play protective or pathogenic roles, but the factors inducing their trigger are still uncertain<sup>6</sup>. In particular, the effect of biological treatments, extensively used in SARD management, on anti-DFS70 antibodies expression has not yet been investigated and thus represents an intriguing matter. Despite a vast amount of data supporting a role of anti-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) agents in the occurrence of immunogenicity<sup>7</sup>, no data were available about these drugs' effect on the occurrence of anti-DFS70 antibodies. In addition, the induction of autoimmune phenomena such as the drug-induced lupus erythematosus (DIL) syndrome was reported<sup>7</sup>. To our knowledge, no data regarding the relationship of these adverse reactions and the development of anti-DFS70 antibodies have been published. The aims of our study were first, to investigate the prevalence of anti-DFS70 antibodies in a large cohort of RA and SpA patients, and then to evaluate the effects of anti-TNF- $\alpha$  therapies on their development.

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Basilicata before the start of the study (705/2017). Informed consent was obtained from all patients included in the study.

We collected serum specimens from 100 adult patients with RA<sup>8</sup> (87 female:13 male; mean age  $55.4 \pm 11.7$  yrs; mean disease duration  $14.4 \pm 9.9$  yrs), and 105 patients with SpA<sup>9</sup> (50 female:55 male; mean age  $54.0 \pm 15.0$  yrs; mean disease duration  $18.2 \pm 18.7$  yrs) who attended the Rheumatology Institute of Lucania, Italy. Demographic and clinical data were obtained from medical records. Sera were tested for antinuclear antibodies (ANA) by indirect immunofluorescent (IIF; HEp-2000 Fluorescent ANA-RoTest System, Immuno Concepts), for anti-DFS70 antibodies by immunoblotting (IB; Alphadia, Wavre) and for anti-extractable nuclear antigen (ENA) autoantibodies by chemiluminescence (LIAISON XL, Diasorin).

We observed the nuclear DFS-IIF pattern in 11/100 RA and in 10/105 SpA serum samples, respectively. Four of 100 RA (4.0%) and 4/105 SpA patients (3.8%) were also positive against DFS70 by IB. All anti-DFS70-positive RA samples showed anti-ENA negativity while 1/4 SpA samples was also positive for anticentromere specificity. The frequencies of anti-DFS70 antibodies in both disease groups revealed no statistical differences ( $p > 0.05$ ). In both groups, no significant differences were found between patients with and without anti-DFS70 antibodies in female:male ratio, disease duration, and mean age ( $p > 0.05$ ). We also investigated the possible associations of anti-DFS70 antibody presence with clinical features or certain manifestations in both cohorts (Table 1). Interestingly, in the SpA group, all anti-DFS70-positive patients had a psoriatic arthritis (PsA) diagnosis. For each disease, we evaluated the effects of biologic agents on the occurrence of anti-DFS70 antibodies and ANA. In RA, 13 patients were ANA-positive at baseline and 1 was anti-DFS70-positive. ANA became positive after anti-TNF- $\alpha$  therapy in 36% (18/50) of the treated patients ( $p < 0.05$ ; OR 0.27, 95% CI 0.12–0.60); 16.7% (3/18) of them showed anti-DFS70 pattern. In SpA, 8 patients were ANA-positive at baseline, while ANA became positive after anti-TNF- $\alpha$  therapy in 35.8% (24/67) of patients ( $p < 0.05$ ; OR 0.15, 95% CI 0.06–0.36); 12.5% (3/24) of them were anti-DFS70 positive (Table 2). Notably, 1 SpA patient, ANA-negative at the

Table 1. Serological and clinical data of anti-DFS70-positive patients.

Patient	Diagnosis	ENA	Extraarticular Manifestations	Comorbidity
1	RA	–	None	AH
2	RA	–	None	EM
3	RA	–	Lung fibrosis	OP, AH, HBV, DM, Dyslipidemia
4	RA	–	None	None
5	SpA	–	Erythema nodosum	Autoimmune thyroiditis
6	SpA	–	None	COPD, AH
7	SpA	–	Psoriasis	COPD, autoimmune thyroiditis, allergic asthma
8	SpA	+	Psoriasis	Autoimmune thyroiditis

Anti-DFS70: anti-dense fine speckled 70; ENA: extractable nuclear antigen; RA: rheumatoid arthritis; SpA: spondyloarthritis; AH: arterial hypertension; EM: endometriosis; OP: osteoporosis; HBV: hepatitis B virus; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease.

Table 2. Effect of anti-TNF- $\alpha$  treatment on ANA and anti-DFS70 antibody occurrence in patients with SpA and patients with RA.



		T0 (Baseline)	T1 (after anti-TNF- $\alpha$ treatment)
RA, n = 100	ANA-positive	13/100 (13.0)	18/50 (36.0)
	Anti-DFS70-positive	1/13 (7.7)	3/18 (16.7)
SpA, n = 105	ANA-positive	8/105 (7.6)	24/67 (35.8)
	Anti-DFS70-positive	0/8 (0.0)	3/24 (12.5)

Values are n (%). TNF: tumor necrosis factor; ANA: antinuclear antibodies; anti-DFS70: anti-dense fine speckled 70; SpA: spondyloarthritis; RA: rheumatoid arthritis.

first evaluation and treated with conventional disease-modifying antirheumatic drugs, developed the anti-DFS70 antibodies during the followup after a diagnosis of prostate cancer. No anti-DFS70-positive patients developed DIL while under treatment with anti-TNF- $\alpha$  therapy.

To our knowledge, this is the first study investigating the prevalence of anti-DFS70 antibodies in a large cohort of patients with RA or SpA together with the effect of TNF- $\alpha$  blockers on their occurrence. In our RA cohort, we found a higher prevalence of anti-DFS70 antibodies positivity than the overall frequencies previously published<sup>8,10</sup>. Our findings in the SpA group showed a comparable prevalence. All anti-DFS70-positive SpA patients had a PsA diagnosis, thus all AS patients were anti-DFS70-negative according to previous evidence<sup>5</sup>. Interestingly, unlike findings in other SARD, the majority of anti-DFS70 antibodies in RA and SpA showed isolated reactivity. Our results on ANA induction by the TNF- $\alpha$  blockers are in agreement with those obtained in previous studies<sup>7</sup>. The strength of our study is the evaluation of the anti-DFS70 antibodies induction rate occurring after anti-TNF- $\alpha$  therapy, resulting in 6.0% and 4.5% of ANA-negative treated RA and SpA patients, respectively. Noteworthy in our cohorts, the majority of anti-DFS70 antibodies were negative before initiating biologics and were induced by anti-TNF- $\alpha$  agents. The exception of 1 SpA patient with prostate cancer history is supported by previous studies showing that the anti-DFS70 antibodies were significantly predominant in sera from prostate cancer patients compared to matched controls<sup>1</sup>.

The most significant result is that anti-DFS70 antibodies do not have a pathogenetic role, as supported by all the study findings. Owing to the low number of anti-DFS70-positive patients, further multicenter studies are required to validate these preliminary data.

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