

## Effects of tumour necrosis factor- $\alpha$ inhibitors in mothers and daughters concordant for HLA-B27-positive ankylosing spondylitis

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### ABSTRACT

**Objective.** *Pharmacogenomics is considered as the new frontier to predict the response to treatments and it can also be based on the comparison of family members being treated for the same condition. No data are available on the impact of anti-tumour necrosis factor (TNF)- $\alpha$  therapies in members of the same family with ankylosing spondylitis (AS).*

**Methods.** *We describe three mother-daughter couples concordant for AS and HLA-B27, both treated with TNF- $\alpha$  inhibitors, for whom the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP were evaluated during a follow-up of 24 months.*

**Results.** *All patients manifested improvements of all scores, but the daughters had a more prominent effect achieving faster complete disease remission.*

**Conclusion.** *We hypothesise that longer standing chronic inflammation and older age may cause a less prompt and effective response to treatment in SA when compared with their genetically related controls.*

### Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterised by the elective involvement of axial and peripheral joints and entheses, causing axial fusion, severe functional impairment and ultimately disability, which can be considered a prototype of immune-mediated inflammatory rheumatologic disorders grouped under the term spondyloarthritis (1). The diagnosis of AS has recently improved in specificity and sensibility thanks to new criteria and magnetic resonance imaging (2, 3). At the same time, therapy has evolved due to the growing understanding of the pathogenetic mechanisms of the disease, involving dysfunction and oversecretion of multiple pro-inflammatory molecules, in particular tumour necrosis factor (TNF)- $\alpha$  (4). As a consequence, the recent introduction of TNF- $\alpha$  blockers opened a new era for patients with AS, with dramatic improvements

of their outcomes (5). These agents include adalimumab and etanercept that are effective in both reducing disease activity and controlling disease progression; moreover, their safety has been largely documented both in AS as well in other spondyloarthritis (5-8). Notably, there are limited data on individual predictors and pharmacogenetic determinants of response. Nonetheless, data from same-sex relatives with AS being treated with TNF- $\alpha$  inhibitors are unique models to estimate the importance of these factors. We report herein data on the effects obtained with these treatments on AS in three mother-daughter pairs and describe for the first time that younger relatives (*i.e.* daughters) may manifest a better response.

### Patients and methods

We evaluated three mother-daughter couples, with an established diagnosis of AS based on the Assessment of Spondyloarthritis International Society (ASAS) Classification Criteria (2), all attending the outpatient clinic of the University of Siena in Italy. All 6 patients carried the human leucocyte antigen (HLA)-B27 allele.

The three couples of patients were treated with anti-TNF- $\alpha$  therapies; one received adalimumab (ADA) 40 mg subcutaneously biweekly and two received etanercept (ETN) 50 mg subcutaneously once weekly.

All subjects were evaluated at baseline and every 6 months thereafter, with a global physical examination and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), using 1-10 score for each item (9); the Bath Ankylosing Spondylitis Functional Index (BASFI), using a 1-10 score (10); the Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP (11) were assessed at each time point until the 24<sup>th</sup> month.

### Results

Demographic and clinical data of patients studied are summarised in Table I, showing higher baseline ASDAS-CRP and BASFI values in mothers. During treatments, data in mothers demonstrated a decline in ASDAS-CRP from 3.3 $\pm$ 0.26 to 1.50 $\pm$ 0.46; BAS-

**Table I.** General and clinical data of our three couples of patients with ankylosing spondylitis treated with anti-tumour necrosis factor- $\alpha$  agents.

	Family n. 1			Family n. 2			Family n. 3											
	Mother	Daughter		Mother	Daughter		Mother	Daughter										
Age at onset of symptoms (years)	40	38		21	40		15	14										
Age at diagnosis (years)	70	38		68	44		44	14										
Age at starting biologic therapy (years)	73	39		69	45		45	15										
Previous therapies	NSAIDs, MTX (10 mg weekly)	SSZ (2000 mg daily)		Corticosteroids, MTX (10 mg weekly)	MTX (10 mg weekly)		MTX (15 mg weekly)	NSAIDs										
Biologic therapy (dosage)	ADA (40 mg biweekly)	ADA (40 mg biweekly)		ETN (50 mg weekly)	ETN (50 mg weekly)		ETN (50 mg weekly)	ETN (50 mg weekly)										
Concomitant DMARDs	MTX (10 mg weekly)	None		None	None		MTX (15 mg weekly)	None										
Indices value	ASDAS-CRP	BASFI	BASDAI	ASDAS-CRP	BASFI	BASDAI	ASDAS-CRP	BASFI	BASDAI	ASDAS-CRP	BASFI	BASDAI	ASDAS-CRP	BASFI	BASDAI	ASDAS-CRP	BASFI	BASDAI
Time 0	3.5	6.8	8.2	2.9	2.7	7.3	3	6.1	7.5	2.8	2.3	7.1	3.4	6	7.6	7	1.6	7
Time 6	2.5	6.6	6.3	1.3	1.6	6	2.5	4.1	6	1.4	1	4	2.7	3.9	4.5	3.4	0	3.4
Time 12	1.9	5.8	3.4	1.2	0	3	2.2	3.7	3.1	0.4	0	2.2	1.2	3.6	2.2	1	0	1
Time 24	1.8	6	4.5	0.8	0	1.5	1.4	3.9	4	0	0	0	1.3	3.3	2.5	0	0	0

NSAIDs: non-steroidal anti-inflammatory drugs; MTX: methotrexate; SSZ: sulfasalazine; ADA: adalimumab; ETN: etanercept; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

DAI from  $7.76 \pm 0.38$  to  $3.67 \pm 1.04$ ; and BASFI from  $6.3 \pm 0.44$  to  $4.40 \pm 1.41$ . Nonetheless, at 24 months all mothers had persistent peripheral arthritis, requiring combined therapy with methotrexate and/or oral or intra-articular corticosteroids. On the other hand, daughters achieved a faster decrease of ASDAS-CRP from  $2.63 \pm 0.38$  to  $0.27 \pm 1.04$ , BASDAI from  $7.13 \pm 0.15$  to  $0.70 \pm 0.75$ , and BASFI from  $2.2 \pm 0.56$  to 0. Finally, we observed that at 12 months one daughter stopped the treatment with ETN for complete remission, that persisted for additional 12 months; the other two continued on ADA and ETN for the whole follow-up period.

## Discussion

Occurrence of AS in family members is widely recognised, along with the strong association with the HLA B27 allele (1, 12-14)

In fact, AS occurs in 18.6 to 22.7% of first-degree relatives of probands from International series while the familial prevalence in Italian cohorts ranges between 7.9% and 15.8% (13). From a clinical standpoint, Almodóvar *et al.* analysed the phenotype differences between familial and sporadic AS in 1316 patients (75% men), and reported a higher prevalence of women

and HLA-B27 in the familial variant. In addition, patients with familial AS were younger at disease onset and had worse outcomes compared to the sporadic counterpart (15). However, only a small proportion of 5–8% of HLA-B27 positive individuals of the general population develops ankylosing spondylitis (16). Further studies suggest that women have a more severe disease when this is found in first-degree relatives in comparison with men (17). In particular, despite fewer spinal radiographic changes, women have significantly worse functional outcomes, more aggressive peripheral arthritis, more frequent disability, and major use of combined systemic therapies (17). These data confirm the need of further studies aimed at evaluating the interplay between therapeutic options, particularly with anti-TNF- $\alpha$  drugs, and the role of sex and genetic background. This is of particular importance for biologics, in which economic factors as well as the narrow safety profile encourage a careful discrimination of patients with the highest chances of disease remission. As this is the case, familial AS cases in which both relatives receive the same treatment are a model to estimate the importance of individual factors in determining the re-

sponse to medical therapy. Prototypical examples that could clarify the weight of individual factors in influencing the response to biologics are represented by hereditary autoinflammatory diseases. In these conditions, even if relatives have a similar genetic and clinical background, they achieve the outcomes in different way under the same biological therapy (18). In addition, other arthritides, such as rheumatoid arthritis and juvenile idiopathic arthritis, could represent additional ideal models for evaluating the impact of individual factors on outcomes (19).

We report herein the clinical outcome of three HLA-B27 concordant mother-daughter couples with AS treated with the same anti-TNF- $\alpha$ . At all visits during the 24-month follow-up, all patients had significant improvement, as expressed by the reduction of BASDAI, BASFI and ASDAS-CRP scores, and this was more prominent and faster in daughters compared to mothers.

We are convinced that the present observation is of note to support the importance of early diagnosis and therapy initiation in AS, as age and disease duration appear to influence the response to biologics when genomically similar individuals are compared. In addition, few data on the withdrawal of medical

therapies in axial spondyloarthritis are available. An improved information on this field could derive by studies on familial cases (20).

In the mothers described in this report, the onset of relevant symptoms dated back as long as 50 years before starting anti-TNF- $\alpha$  treatment, and this long-lasting disease process may be considered critical in causing the less prompt and effective response to treatment. On the other hand, although familial AS has greater severity and worst outcome in women, the three cases observed of mother/daughter suggest that anti-TNF- $\alpha$  therapy obtains a significantly better outcome with complete remission of the disease in daughters.

In conclusion, we firmly believe that starting early an adequate anti-TNF- $\alpha$  therapy might modify the probability and rapidity of clinical response and that the shared clinical response in first-degree relatives may be secondary to similar pro-inflammatory mechanisms.

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