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The evolution of spondylarthritis – a therapeutic challenge

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ABSTRACT

We are presenting the case of a 36 years old male diagnosed at the age of 20 with reactive arthritis and at 27 years with ankylosing spondylitis. During the course of the disease, the patient followed treatment with non-steroidal anti-inflammatory drugs, Sulfasalazine and biological therapy. The first two anti-TNF had a very good response. During Adalimumab therapy the patient conceived a child without any teratogenic effect on it. The effect of the two anti-TNF has been long-lasting, but the effectiveness has decreased on the other two. The future of this patient lies in blocking a new molecule in ankylosing spondylitis named IL-17, so we are expecting the disease response to the new biological introduced into ankylosing spondylitis, named Secukinumab.

Keywords: spondylarthritis, anti-TNF, Secukinumab

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, multisystem inflammatory disorder primarily involving the sacroiliac (SI) joints and the axial skeleton, including also peripheral arthritis, enthesitis, and extra-articular organ involvement (1-4). The age of onset of AS is usually from the late teens to age 40 years (5). Prevalence rates of AS are approximately equal in men and women. However, men have more severe radiographic changes in the spine and hips than women (6).

Long-term treatment goals are to maximise quality of life through control of signs and symptoms, prevention of structural damage and preservation of physical function (7).

The introduction of tumour necrosis factor (TNF)-blocking therapy has revolutionized the management of ankylosing spondylitis (AS) over the last decade. However, up to 40% of patients do not respond to or cannot tolerate TNF inhibitors, (8) and loss of efficacy can occur over time (9). Not many studies were performed in case of failure of more than two anti-TNF, but it seems that the lack of two anti-TNF is predictive of the ineffectiveness of the third anti-TNF.

New therapeutic targets are expected in our patient's case to improve the signs and symptoms of the disease improving health-related quality of life.

CASE PRESENTATION

We are presenting the case of a 36 years old male with disease onset at the age of 17 with bilateral metatarsophalangeal II arthritis, interpreted as gout. At the age of 20, after a diarrheal episode, presents left knee arthritis and bilateral metatarsalphalangeal II arthritis. Biologically presents inflammatory syndrome, anti-Yersinia antibodies + and slight condensation of the left iliac joints versus right at basin radiography. The diagnosis was reactive arthritis; antibiotics, non-steroidal anti-inflammatory and Sulfasalazine up to 2 g/day were recommended, discontinued by the patient after 2 months.

In 2007, the patient presented to the St. Mary's Clinical Hospital with chronic inflammatory back pain, bilateral knee arthritis, inflammatory syndrome and negative HLA B27. The diagnosis was peripheral spondylarthritis and the treatment given was with Sulfasalazine up to 2.5 g/day, but the

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treatment was stopped by the patient after 2 months.

Between 2008 and 2009 at "Dr. Carol Davila" Central Military Emergency the patient is treated with Remicade, stopped due to loss of response (medical data not available).

In May 2013, the patient presented in our clinic with severe inflammatory cervical and lumbar pain, arthralgias of the elbows, knees, ankles and metatarsophalangeal. He had already developed modified mobility indices, anterior projection of the cephalic extremity with thoracic kyphosis, ankylosis in elbow flexion, ankle semiankylosis. The disease was very active: ESR 70 mm/h, CRP 110.7 mg/l, BASDAI = 8.75, with chronic sacroilitis (left > right) and acute (right> left) on MRI, so we decided to start Adalimumab. After 3 months he had no clinical symptoms, no inflammatory syndrome and BASDAI = 1. The disease was in remission until March-April 2016 when, despite maintaining the clinical benefit of anti-TNF, a slight increase in C reactive protein was observed, with the occurrence of a psoriasiform exanthema in the calves. Anti-Humira antibodies were negative and acid-serum drug level was at the lower limit of normal. The patient announces that he is the father of a four months healthy baby.

In September 2016 the patient had high disease activity (BASDAI = 4.5, BASDAI-CRP = 3.5), inflammatory syndrome and aggravation of psoriasis lesions. He was switched on Enbrel with insufficient response at the 6-month evaluation and the spread of psoriasis lesions (Fig. 1). The patient was switched on Golimumab. A psoriasiform eruption biopsy was taken by the dermatologist, the diagnosis was anti-TNF-induced psoriasis. The patient performed 10 UVB rays with the disappearance of psoriasis lesions.

At the 3-month assessment (May 2017), disease activity persists (BASDAI = 8.6, ASDAS-CRP = 6.44) with a major inflammatory syndrome (ESR = 89 mm/h, CRP = 273.78 mg/L). The patient doesn't show signs of infection or other changes in laboratory tests including negative hepatitis and Quantiferon.

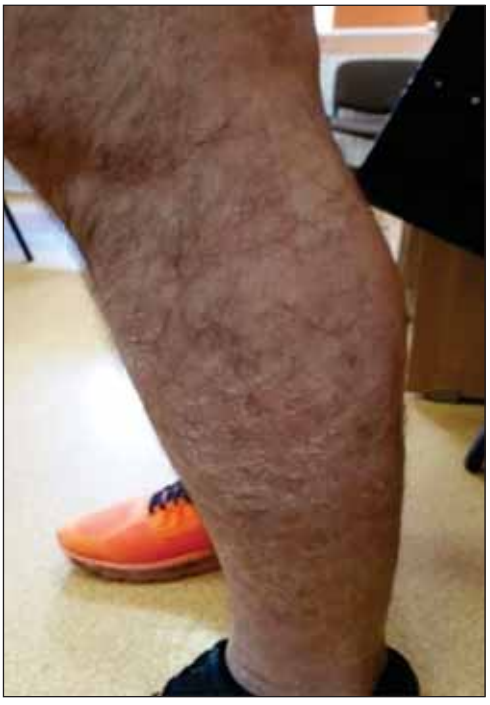

***FIGURE 1**. Psoriatic lesions*

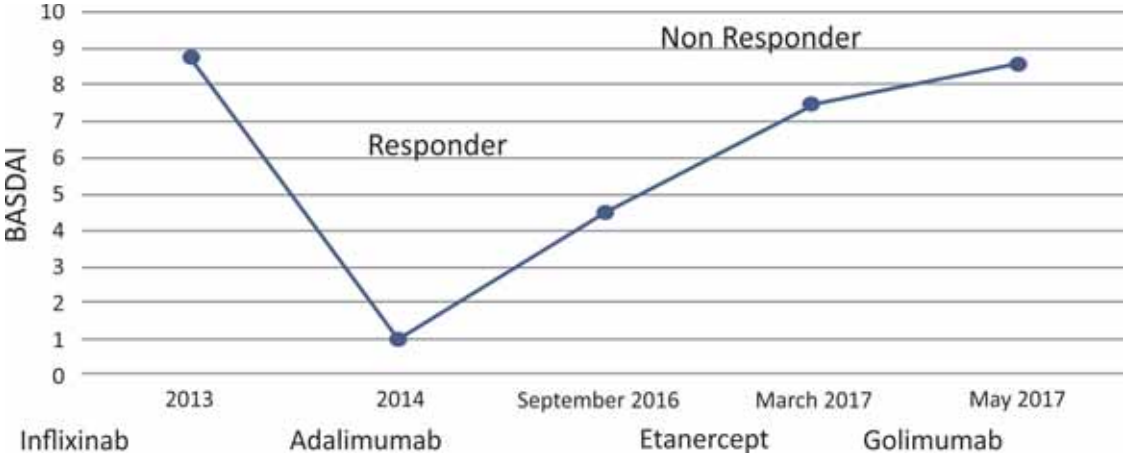

***FIGURE 2.** The evolution of BASDAI during the biological treatment: It is noticeable that during the first two anti-TNF, the patient lost inefficiency after longer time, while in the case of the other two efficacy decreased much faster*

Due to the fact that the patient is a failure on four anti-TNF, we decided to change the biological class to Secukinumab (Fig. 2).

DISCUSSIONS

Anti-TNF-Alpha-Induced Psoriasis – An Unusual Paradox

Our patient developed a psoriasiform eruption during Adalimumab treatment, worsened during Etanercept treatment. The question that raised up was if the patient had psoriatic arthritis with no previous eruption or if the eruption was a dermatological side effect of anti-TNF-alpha treatment? However, several aspects of this phenomenon provide evidence for the idea that it is a side effect of anti-TNF-α agents: absence of a personal or family history of psoriasis, the temporal relationship between anti-TNF-α treatment and the appearance of cutaneous lesions, and the clinical improvement observed after discontinuation of therapy.

Since an initial report in 2003 (10) numerous cases of typical psoriasis and psoriasiform lesions induced by anti-TNF-alpha therapy have been described, and two systematic literature reviews have been performed, the most recent analysing 207 cases (11). This paradoxical side effect has been described in nearly all conditions treated with anti-TNF and with all anti-TNF agents (12,13). The time between anti-TNF-α administration and development of psoriatic lesions varies widely (13) suggesting that an environmental trigger may also be involved. The reported cutaneous lesions are plaque, pustular (50%) or guttate-type psoriasis. The most frequently affected areas are the scalp and flexures and palmoplantar areas (14). The incidence rate of psoriasis in an rheumatic diseases population from the UK was estimated at 1.04/1,000 person-years (15). Data from the Spanish biological register found similar results, with a global incident rate of 2.31/1,000 patient-years (16).

The mechanism underlying the induction or exacerbation of psoriatic lesions by anti-TNF-α antagonists is not clear (17). The most popular is a disequilibrium in cytokine balance. TNF-α suppresses the development of plasmacytoid dendritic cells (pDCs), a major cellular component for the production of IFN type I such as IFN-α (17-19). IFN-α is an inducer of certain chemokine receptors on T cells (CXCR3) that induce T-cell migration to the skin (17-19). Polymorphisms of genes involved in cytokine production, such as IL-23-R, are also probably involved (17).

Biopsy should be considered in all patients with new-onset psoriatic lesions to eliminate differential diagnosis for psoriasis mimickers. A triggering event including infection, a stressful life or intake of new drugs must be systematically investigated. In our case, the diagnosis was confirmed by skin biopsy, the eruption correlated with a major stress in patients life. According to Collamer's algorithm (14), patients with psoriasis covering < 5% of body surface area should be treated with topical treatments (corticosteroids, keratolytics and vitamin D analogs); for lesions covering > 5% of body surface area and palmoplantar disease, topical therapies, occlusive therapy and UV phototherapy should be given. However, in the severe cases, treatment should include both withdrawal of anti-TNF and consequent treatment of psoriasis. In our case, topical steroids, PUVA and switching antiTNF lead to psoriasis resolution.

Fertility and pregnancy safety of antiTNF-alpha medication

Little is known about anti-TNF use in males with rheumatic diseases that want to conceive. Several studies have sought to determine the impact of anti-TNFα medications on sperm viability (20-22).The most recent study confirms that sperm quality in patients with active AS and after receiving short- and long-term TNF-α blocker therapy is comparable to sperm quality in healthy controls (20). A total of 17 pregnancies conceived by men taking Infliximab have been reported (21). One pregnancy resulted in a first trimester miscarriage in a woman with Addison's disease and a prior miscarriage. The remaining pregnancies resulted in healthy babies. These reports suggest that the anti-TNFα medications promoted male fertility with no harm for the babies. According to recent EULAR recommendations, continuation of TNF inhibitors in female patients during the first part of pregnancy should be considered (23). Etanercept and Certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage (23). Infliximab and Adalimumab may preferentially be stopped at 20 weeks and Etanercept at week 30-32 of pregnancy. Sound

evidence for fetal/child safety is still lacking for biologics approved less <5 years ago (23). Current evidence for Adalimumab indicates no increased risk for congenital malformation and can be continued up to gestational week 20, if indicated can be used through pregnancy and is compatible with breastfeeding (23).

TNF non-responders – a sad but hopeful story

Around 10-30% of patients do not respond to initial anti-TNF treatment and 23-46% of patients lose response over time (24,25). A common mechanism for the loss of response is immunogenicity due to the formation of antibodies against the TNFα antagonists. Primary nonresponse refers to patients who do not respond adequately to the initial loading doses of a biologic agent (25,26). These patients are found to have adequate drug levels and no antibodies. They may not respond to the particular mechanism of action of the drug, and switching to a medication in a different class is recommended (25,26), Secondary loss of response refers to patients who had previously responded to a biologic agent. The drug dosing should be increased if drug levels are low and antibodies are not present, switched to another drug in the class if drug levels are low and antibody levels are high, or switched to another drug mechanism if drug levels are high and antibodies are not present (25,26). Observational studies have demonstrated ADA levels > 4.5 mcg/ml are associated with an increased likelihood of maintaining response (27,28). For our patient Adalimumab serum level was 7.5 mcg/ml, although the cutoff for was 10 mcg/ml. No anti-Adalimumab antibodies were present but the drug level was low suggesting that antibodies might be present but under the limit of detection.

Yanai et al. (26) have shown that patients with no/low-titer ADA responded significantly better to dose intensification (increase in the dose or dose frequency) compared with the anti-TNF switch. Still, this strategy is not approved for patients with AS, so our option at that moment was several anti-TNF switches. Several studies have confirmed the efficacy of switching to a second or third TNFi although overall effectiveness seems to be somewhat lower than in non-switchers (29, 30). No data are available regarding the third and fourth anti-TNF switch.

There is significant unmet need in patients with ankylosing spondylitis who have inadequate response or intolerance to anti-tumour necrosis factor treatment. Secukinumab, an anti-interleukin-17A monoclonal antibody, significantly improved signs and symptoms of AS in the MEASURE 1 and MEASURE 2 study (31). Around 30% patients were not anti-TNF naive. Up to 60% of anti-TNF inadequate responders had achieved ASAS20 response by 52 weeks (31). Recently, longer term 2-year data were available, demonstrating that Secukinumab provided sustained improvements in signs and symptoms of AS, with improved physical function regardless of anti-TNF status (31).

CONCLUSIONS

AntiTNF-α therapies are effective for induction and maintenance of remission in patients with ankylosing spondylitis, allowing young male patients to have a normal social and family life. However, clinicians face many challenges in determining the best course of action when a patient loses response or develops side effects. When patients are found to have continued active inflammation despite having undergone biologic therapy, the first determination should be whether this represents a primary nonresponse to the drug's mechanism of action or a secondary loss of response due to inadequate drug levels and/or antibody formation to the drug. In this cases, new treatment options like anti IL17 antibodies have just became available.

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