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SHORT COMMUNICATION - OBSERVATIONAL RESEARCH

Drug levels, immunogenicity and assessment of active sacroiliitis in patients with axial spondyloarthritis under biologic tapering strategy

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Abstract The aim of the study was to assess drug levels, immunogenicity and sacroiliitis on MRI in patients with axial spondyloarthritis under biologic tapering strategy. Consecutive patients with axial spondyloarthritis who remained in low disease activity more than 1 year after dose tapering of infliximab and adalimumab were included. Plasma drug concentrations of TNF inhibitors and anti-drug antibodies were determined, and MRI of sacroiliac joints was evaluated. Of twenty patients included, eighteen had therapeutic drug levels, no patient had anti-drug antibodies, and no patient had active sacroiliitis on MRI. These data could support the biologic tapering strategy and their maintenance over time.

Keywords Biologic tapering strategy · Axial spondyloarthritis · Immunogenicity · Active sacroiliitis

Introduction

The efficacy of tumor necrosis factor-α inhibitors (anti-TNF-α) in the treatment of axial spondyloarthritis, including ankylosing spondylitis (AS), is well known [1–3], but there is less evidence on dose tapering of biologic drugs in patients in clinical remission or low disease activity (LDA) [4–7]. The published studies have evaluated clinical response after dose tapering of biologics, but they have not evaluated other important aspects like plasma drug concentrations, development of anti-drug antibodies or presence of active sacroiliitis on magnetic resonance image (MRI) [4–7].

It is unknown whether dose tapering of biologic drugs can result in low drug levels or development of anti-drug antibodies. Some studies have found association between low infliximab and adalimumab trough levels, development of anti-drug antibodies and worse clinical response in AS patients [8, 9]. Immunogenicity does not seem to influence treatment with etanercept in AS patients [10].

Several studies have shown that treatment with anti-TNF at standard doses reduce bone edema in sacroiliac joints in MRI in patients with axial spondyloarthritis [3, 11, 12]. No studies evaluated the sacroiliac joint inflammation in patients with tapered doses of biologics. One study evaluated the effects of low doses of infliximab (3 mg/kg/every 8 weeks) in spinal inflammation in patients with AS, showing a significant reduction, but MRIs of sacroiliac joints were not made [13].

The aim of this study was to assess anti-TNF levels, immunogenicity (development of anti-drug antibodies) and active sacroiliitis on MRI in patients with axial spondyloarthritis remaining in LDA more than 1 year after dose tapering of biologic drugs, infliximab and adalimumab.

Materials and methods

This was an observational cross-sectional study. From June to December 2014, all consecutive patients with axial spondyloarthritis fulfilling Assessment of SpondyloArthritis international Society, ASAS, criteria [14], including AS, at the department of Rheumatology of Hospital del

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Table 1 Characteristics of patients with axial spondyloarthritis more than 1 year after dose tapering of biologic drugs

Demographic and clinical characteristics	Patients with axSpa in dose tapering strategy (20)
Age, mean ± SD (years)	47 ± 13.81
Male, number (%)	16 (80 %)
Current smokers, number (%)	11 (55 %)
Ankylosing spondylitis, number (%)	17 (85 %)
HLAB27+, number (%)	18 (90 %)
Peripheral involvement (arthritis and/or enthesitis and/or dactylitis), number (%)	10 (50 %)
Previous uveitis, number (%)	2 (10 %)
Therapy with sDMARD, number (%)	3 (15 %)
Structural damage in spine, number (%)	8 (40 %)
Disease duration, mean ± SD (years)	10.75 ± 6.03
Duration of biologic treatment, mean ± SD (years)	7.4 ± 2.5
Time in dose tapering, mean ± SD (months)	41.65 ± 18.77

axSpa axial spondyloarthritis, *SD* standard deviation, + positivity, *sDMARD* synthetic disease-modifying antirheumatic drugs

Mar (Barcelona), who remained in LDA (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI, less than 4 units) with normal acute phase reactants more than one year after dose tapering of infliximab and adalimumab, were included.

Tapered dosages of biologic drugs were previously administered to patients in sustained remission for a minimum of 6 months without nonsteroidal anti-inflammatory drugs (NSAIDs) consumption. Remission was defined using clinical measures (BASDAI ≤2/10, no peripheral joint disease such as arthritis and/or enthesitis) and biologic measures (C-reactive protein (CRP) levels lower or equal to normal values) according to other reports [5].

We used two dose tapering protocols: lowering the dose of infliximab, 3 mg/kg every 8 weeks, and extending the interval between doses of adalimumab, 40 mg every 3 weeks, like other reports [6, 7].

Plasma drug concentrations of anti-TNF inhibitors (infliximab and adalimumab) and anti-drug antibodies were measured, and MRI of sacroiliac joints was performed in all patients included (consecutive patients with axial spondyloarthritis who remained in LDA more than 1 year after dose tapering).

Plasma drug concentrations and anti-drug antibodies were measured by double-enzyme-linked immunosorbent assay, ELISA, commercialized by Proteomika S. L. [15]. Drug concentrations were measured in microgram per milliliter (μg/ml). Infliximab concentration was therapeutic above 1.5 μg/ml. Antibodies against infliximab were positive above two arbitrary units/milliliter (AU/ml). Adalimumab concentration was therapeutic above 0.8 μg/ml. Antibodies against adalimumab were positive above 3.5 AU/ml. Serum samples were taken just before the drug is administered, when drug levels are presumably at their lowest.

MRI of sacroiliac joints was performed using the superconductive 1.5 tesla system (Signa Excite Echo-Speed II; General Electric Medical Systems). Semicoronal and axial planes and T1 and STIR sequences were obtained. The presence of active sacroiliitis on MRI was evaluated by an experienced reader, MA, according to the ASAS/OMERACT (outcome measurement in rheumatology) group as bone marrow edema on STIR sequences. Bone marrow edema lesions appear as hyperintense signal on STIR sequences located subcondrally and periarticularly. If there is only one lesion, it should be present on at least two consecutive slices. If there is more than one lesion, one slice may be sufficient [16].

The study was approved by the local ethics committee. All patients were required to sign a consent form.

Results

Twenty patients with axial spondyloarthritis who remained in LDA more than one year after dose tapering of biologic drugs, infliximab and adalimumab, were included. There were sixteen patients on adalimumab treatment and four patients on infliximab treatment. The mean time in dose tapering strategy was 41.65 ± 18.77 months. Table 1 shows demographic and clinical characteristics of the twenty patients included.

Eighteen patients had therapeutic plasma levels of anti-TNF. Two patients treated with infliximab had low drug levels but also undetectable levels of antibodies against infliximab. All sixteen patients treated with adalimumab had therapeutic plasma levels.

None of twenty patients had anti-drug antibodies in serum, either against infliximab or against adalimumab

Table 2 Drug levels, immunogenicity and sacroiliitis on MRI more than 1 year after dose tapering of biologic drugs

Patients	Anti-TNF	Drug levels (μg/ml)	Therapeutic drug levels (yes/no)	Antibodies against anti-TNF (yes/no)	BMO in SIJ
1	ADA	10.6	Yes	No	No
2	ADA	1.07	Yes	No	No
3	ADA	1.9	Yes	No	No
4	ADA	5.9	Yes	No	No
5	ADA	3.42	Yes	No	No
6	ADA	4.4	Yes	No	No
7	ADA	1.5	Yes	No	No
8	ADA	4.39	Yes	No	No
9	ADA	1.17	Yes	No	No
10	ADA	1.18	Yes	No	No
11	ADA	7.54	Yes	No	No
12	ADA	3.5	Yes	No	No
13	ADA	2.97	Yes	No	No
14	ADA	2.57	Yes	No	No
15	ADA	4.24	Yes	No	No
16	ADA	4.03	Yes	No	No
17	IFX	2.12	Yes	No	No
18	IFX	1.13	No	No	No
19	IFX	0.02	No	No	No
20	IFX	2.7	Yes	No	No

ADA adalimumab, *IFX* infliximab, μg/ml microgram per milliliter, *BMO* bone marrow edema, *SIJ* sacroiliac joints

(Table 2). The two patients with low infliximab levels remained in sustained remission status.

MRI of sacroiliac joints was performed in all patients, and no patient had active sacroiliitis on MRI according to the ASAS/OMERACT group (Table 2). No patient also had enthesitis, synovitis or capsulitis on MRI.

Discussion

In our series of twenty patients with axial spondyloarthritis who remained in LDA more than one year after dose tapering of biologic drugs, therapeutic plasma levels of anti-TNF were found in most cases (90 %) and anti-drug antibodies and bone edema in sacroiliac joints were not found in any patient.

Our study supports also dose tapering strategy in patients with axial spondyloarthritis in clinical remission or LDA. Some studies have shown that biologic dose tapering was effective in maintaining LDA but have not evaluated plasma drug levels, development of anti-TNF antibodies or presence of active sacroiliitis on MRI [4–7].

In our series, in only two cases low concentrations of anti-TNF were found and anti-drug antibodies were not found in any patients. The absence of immunogenicity in all patients is very important because they were treated with dose tapering strategy a mean time longer than 3 years.

The absence of bone edema on MRI of sacroiliac joints found in our patients supports also this therapeutic strategy because lack of active inflammation was confirmed. Biologic dose tapering maintains LDA over time in most patients [4–7], and MRI can confirm the absence of inflammation in sacroiliac joints more objectively.

The main limitations of the study are the small sample size, the absence of control group, the higher number of patients with AS than with non-radiographic axial spondyloarthritis and the heterogeneous distribution of treatments (more patients treated with adalimumab). These limitations are owed to the study is based on clinical daily practice in a single-center. Other limitations are the two dose tapering protocols, lowering the dose of infliximab and extending the interval between doses of adalimumab, motivated by the drugs presentation, and the different characteristics of the two drugs. Adalimumab is a fully humanized antibody, and infliximab is a chimeric antibody. The humanization process might prolong the half life of the antibody in vivo which could explain why therapeutic plasma levels were found in all patients treated with adalimumab but not in all patients treated with infliximab. However, anti-drug antibodies were not found in any patient regardless of drug administrated.

The therapeutic plasma concentrations of anti-TNF in most cases, the absence of anti-drug antibodies and the absence of active sacroilitis on MRI found in our patients

with axial spondyloarthritis after tapered dosages of infliximab and adalimumab are data that could support the tapering strategy and their maintenance over time. Further studies with larger number of patients are needed to confirm these results.

Compliance with ethical standards

Conflict of interest The authors declare that they have no other conflict of interest.

Ethical approval The study was approved by the local ethics committee.

Informed consent Informed consent was obtained from all individual patients included in the study.

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