

Biologics in relapsing polychondritis: a case series

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ABSTRACT

Objective. To describe the effects of biologics in an unbiased series of relapsing polychondritis cases.

Methods. We extracted all the cases encoded "polychondritis" from the computerised medical files of our department. The relapsing polychondritis diagnosis was confirmed using Damiani's criteria. Patients treated with biologics were evaluated for efficacy and adverse drugs reactions until October 2012.

Results. Nine patients were exposed to 22 biologics as corticosteroid-sparing drugs. Biologics were used at the same doses as in rheumatoid arthritis. Mean duration of exposure to biologics was 28 months. A TNF-antagonist was most frequently used as first-line biologic therapy (7/9), leading to partial or complete efficacy in six cases (85.7%). Loss of efficacy occurred in 5 cases. Abatacept (n=3) and tocilizumab (n=2) were effective as second-line biologic therapy while anakinra (n=2) and certolizumab (n=1) were not. Seven serious adverse drug reactions occurred, including 5 infections.

Conclusion. TNF- α antagonists may be proposed earlier in relapsing polychondritis to spare corticosteroids. Switching to another biologic can be proposed in case of loss of efficacy. Tocilizumab or abatacept can be proposed as third-line therapy. The benefit-to-risk ratio of biologics in relapsing polychondritis should be evaluated prospectively.

Introduction

Relapsing polychondritis (RP) is a rare autoimmune disease characterised by flares of cartilage inflammation involving the ears, nose, trachea, and joints. Ocular or cochlear involvement is not rare, while cardiovascular features (aortitis, valvulopathy) are scarce (1). First-line drugs of RP are corticosteroids. Dapsone and methotrexate have been proposed as second-line therapies (2). Little is known about the efficacy of biologics in RP. The use of TNF antagonists has been most reported. However, only single case reports or case-series not exceeding three patients have been published, totalising 43 patients. Among them, 25 had a complete or par-

tial response to TNF-antagonists (3). There are also very few reports of anakinra or tocilizumab use (3). In 2010, we reported a first case of abatacept use in a RP patient (here, patient 4) (4). Some reports suggested the efficacy of rituximab (5-7), but a 9-patients single-centre case-series did not (8). This suggests that there may be a publication bias favoring successful issues in case-reports. Due to the absence of randomised controlled trial and prospective cohort studies, a systematic retrospective assessment is pivotal to properly assess the efficacy and safety of biologics in RP. This work was aimed at colligating and describing the effects of biologics in all RP patients treated in our department.

Patients and methods

Since 1993, all in- and out-patients of our University Internal Medicine department are registered in a computerised system using a diagnosis code. In June 2012, we performed the extraction of all cases encoded as "polychondritis". Medical files of these patients were reviewed and RP diagnosis was confirmed using Damiani's McAdam-modified criteria (9). All patients treated with biologics were evaluated for efficacy and adverse drug reactions until 31 October 2012 (last follow-up date). Complete response, partial response and no response were respectively defined as the complete disappearance of all the clinical symptoms, the improvement of at least one clinical symptom and the lack of improvement (or the worsening) of all the symptoms according to the physician clinical assessment. We also assessed the corticoid-sparing effect of biologics. Data were collected in the medical files and by questioning patients by phone.

Results

Among 23 patients encoded "RP", 18 fulfilled Damiani's criteria. They also fulfilled McAdam's criteria (10). Among them, 9 were exposed to 22 biologics as corticosteroid-sparing drugs. Clinical characteristics of these patients (3 men and 6 women) are detailed in Table I. Mean age at diagnosis was 44.7 years (range: 36-57). All patients had chondritis and seronegative poly-

Competing interests: none declared.

arthritis, 4 had cochlear or vestibular dysfunction, 2 had ocular inflammation and 1 had aortic valvulopathy. Only one patient had a cartilage biopsy and it was compatible with the diagnosis. None of the patients had mouth ulceration, haematologic disorder, connective tissue disease, other vasculitis or antineutrophil cytoplasmic antibodies. Patient 9 had been suffering from subacute and chronic cutaneous lupus for five years when he developed seronegative arthralgia, nose, auricular and tracheal inflammation. He had no anti-DNA or anti-ENA antibodies. Anti-collagen II and anti-matrilin 1 autoantibodies were not searched.

Mean time from diagnosis to first biologic use was 9 months. Biologics were used at the same doses as in rheumatoid arthritis. Seven patients were treated with one or more TNF-alpha antagonists (adalimumab n=7, etanercept n=4, infliximab n=2, certolizumab n=1), 3 with abatacept, 2 with anakinra and 2 with tocilizumab. Biologics were used in 3 cases (patients 4, 6 and 8) because of a severe, cortico-dependent disease with tracheal inflammation. In the other cases, biologics were prescribed due to a poor tolerance or response to corticosteroids and the patients' wish of a rapidly acting drug. In 6 cases, biologics were started while the patient was also treated with another drug in addition to corticosteroids (methotrexate, n=3; hydroxychloroquine, n=2; dapsone, n=2). In two patients, these drugs were discontinued because of inefficacy when the biologic was started (patients 2 and 5). In the four other patients, the drug was continued while the biologic was introduced because the drug had a significant but insufficient efficacy (dapsone for patient 1, dapsone and methotrexate for patient 4, hydroxychloroquine for patients 3 and 7).

Mean duration of exposure to biologics was 28 months. Efficacy outcomes are detailed in Table II. TNF-antagonists were the most frequent first-line biologic therapy (n=7/9). A partial or complete response was obtained in 6 patients (85.7% of the cases). A loss of efficacy occurred in 4 cases on average at 9.75 months. Remission was then obtained with another biologic. Anakinra

Table I. Demographic characteristics of the 9 relapsing polychondritis patients treated with biologics.

Patient	Age at diagnosis	Sex	Signs of RP	Disease duration before biologics (years)	Treatments before biologics
1	44	Female	Nose, ears, joints, aortic valve	5	CS, HCQ, dapsone
2	57	Female	Nose, ears, joints, cochlea	3.5	CS, MTX, gold salts, AZA
3	37	Male	Nose, ears, joints, cochlea, trachea	1.5	CS, HCQ
4	49	Female	Nose, ears, joints, trachea	6.5	CS, HCQ, dapsone, MTX
5	40	Female	Ears, joints, trachea, eyes	2.2	CS, MTX
6	52	Male	Ears, joints, trachea, cochlea	0.7	CS
7	47	Female	Nose, ears, joints, cochlea, trachea	1.8	CS, HCQ
8	40	Female	Nose, ears, joints, trachea, eyes	1	CS
9	36	Male	Nose, ears, joints	0.3	CS

AZA: azathioprine; CS: corticosteroids; HCQ: hydroxychloroquine; MTX: methotrexate.

Table II. Efficacy of biologics in the 9 relapsing polychondritis patients.

Patient	Drug	Efficacy	Duration (months)	Reason for withdrawal	Corticosteroid withdrawal
1	Etanercept	Partial	3	Insufficient efficacy	No
	Adalimumab	Partial	3	Insufficient efficacy, pain at injection site	No
2	Adalimumab	Yes	15	Loss of efficacy	Yes
	Infliximab	No	0.5	Systemic reaction	-
	Anakinra	No	3	No efficacy, systemic reaction	No
	Abatacept	Partial	12	Insufficient efficacy	No
	Tocilizumab	Yes	7	Ongoing	Yes
3	Etanercept	Yes	12	Loss of efficacy	Yes
	Adalimumab	Yes	26	Inactive disease	Yes
4	Etanercept	Yes	9	Loss of efficacy	Yes
	Adalimumab	Partial	6	Loss of efficacy	No
	Infliximab	Yes	10	Loss of efficacy	Yes
	Anakinra	No	1.5	No efficacy	No
	Abatacept	Yes	33	Minor loss of efficacy	Yes
	Certolizumab	No	3	No efficacy	No
	Abatacept again	Yes	15	Ongoing	Yes
5	Tocilizumab	Yes	10	Ongoing	Tapering
6	Adalimumab	Yes	20	Inactive disease	Yes
7	Adalimumab	Yes	65	Ongoing	Yes
8	Adalimumab	-	0	Systemic reaction at 1 st injection	-
	Etanercept	Yes	3	Ongoing	Tapering
9	Abatacept	Partial	3	Subacute cutaneous lupus flare	No

(n=2) and certolizumab (n=1) were not effective. Tocilizumab and abatacept induced a complete (3/5) or partial response (2/5) in all cases. Corticosteroids have been withdrawn in 4 patients on average at 8 months (range 3-16) and have been tapered from 60 mg (range: 80-40 mg) to 10.8 mg (range: 15-7.5 mg) (-82%) in 3 others.

Seven drug-related adverse drug reactions occurred: reaction at injection site in 3 patients (1 on anakinra, 2 on adalimumab) and infections in 3 patients: 1 pneumonia on adalimumab (patient 7), sinusitis and otitis followed by herpes zoster on tocilizumab (patient 5) and cellulitis on abatacept (patient 4). Patients fully recovered without sequelae.

Discussion

The pathophysiology of RP remains obscure. Autoimmunity is implicated, involving both autoreactive TH1-cells and B-cells producing autoantibodies directed against cartilage components such as type II collagen or matrilin 1 (11). However, the rationale for the use of biologics in this disease relies essentially on clinical experience.

In this series, all biologics but anakinra and certolizumab had a consistent effect. Rituximab was not used. TNF antagonists have demonstrated their efficacy in every feature of RP. In our patients, they lead to a higher rate of complete or partial remission than in published case-reports. Notably, infliximab was the drug used in 34/43 of the published cases while we rarely used it (3). We favoured the use of subcutaneous antagonists for practical reasons. These were particularly effective in our patients, and they may have contributed to a higher patients' autonomy and to reduced costs by avoiding hospitalisations. Loss of efficacy occurred frequently but switching from a TNF-alpha antagonist to another TNF-alpha antagonist was frequently effective. To our knowledge, assessment of such switches has not been published.

Contrarily to the majority of the published case-reports (3), anakinra was not effective in 2 patients. Tocilizumab as well as abatacept was remarkably effective. Concerning tocilizumab, severe infections occurred in one patient after the first and the third infusions while the patient had suffered no infection during the preceding two years despite high corticosteroid doses and exposure to methotrexate. However, the drug was so efficacious that the patient refused to stop it. For this patient, tocilizumab had been preferred to TNF alpha antagonists because she had been

treated one year before for a localised breast cancer and the guidelines of the French Rheumatology Society recommend avoiding TNF blockers in such patients. The efficacy of tocilizumab in RP has been previously reported in only two reports (12, 13).

Albeit retrospective, the strength of our study is the systematic search of biologic-treated RP patients, avoiding any publication bias. All the cases described here were validated using the Damiani's criteria, while those described in the literature corresponded to heterogeneous conditions. Similarly, efficacy outcome definitions are heterogeneous in previously published cases. We choose here clinical and simple definition. In future, the RP Disease Activity Score, recently proposed, should be preferentially used particularly in prospective studies (14). Furthermore, the long-term follow-up for the majority of the cases allowed describing the effect of exposure to several lines of biologics in a same patient. Encoding errors leading to the non-selection of RP patients seem unlikely as chondritis is a major symptom for physicians trained in systemic diseases. Nevertheless, RP is often a difficult-to-diagnose condition and such errors cannot be fully ruled out.

In conclusion, TNF-antagonists seem to be effective, rapidly acting drugs for second-line therapy in RP. Switching from a TNF-antagonist to another yielded good results and may be proposed before using tocilizumab or abatacept. TNF-antagonists may be proposed earlier in the disease course as corticosteroid-sparing drugs. However, we have concerns on the frequency of infectious complications, so the benefit-to-risk ratio of biologics compared with immunosuppressive drugs in RP deserves to be prospectively evaluated.

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