Extraarticular Manifestations of Rheumatoid Arthritis Develop in Patients Receiving Anti-Tumor Necrosis Factor-α Treatment: A Retrospective Chart Review from a UK Center

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ABSTRACT. ***Objective.*** To assess the evolution of preexisting extraarticular manifestations of rheumatoid arthritis (EA-RA) in patients treated with anti-tumor necrosis factor-α (TNF-α), as well as the development of new EA-RA.

Methods. We assessed EA-RA in 152 patients receiving anti-TNF-α treatment.

Results. In 22 cases, a new EA-RA developed. In 5 cases, there was evidence of progression of preexisting EA-RA. Regression was found in 4 cases. Some patients were in disease remission when they developed EA-RA, whereas some patients had moderate/high disease activity.

Conclusion. EA-RA are still present in patients treated with anti-TNF-α. Development of new severe EA-RA is rare in patients receiving anti-TNF therapy. (J Rheumatol First Release Sept 1 2014; doi:10.3899/ jrheum.131026)

Key Indexing Terms:
EXTRAARTICULAR MANIFESTATIONS TUMOR NECROSIS FACTOR-α
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Morbidity and mortality in patients with rheumatoid arthritis (RA) are mainly increased by extraarticular manifestations (EA-RA). Studies have suggested that only patients with RA who have systemic manifestations, as opposed to patients with RA without systemic manifestations, have an increased mortality when compared with the general population[1,2]. The prevalence of systemic manifestations reported in studies of RA is about 8% to 12%[1,2,3,4]. EA-RA is associated with increased disease activity and markers of inflammation, such as high levels of rheumatoid factor (RF) and C-reactive protein[4,5,6].

We report here a clinic-based study in which we assessed the evolution of preexisting EA-RA in patients treated with anti-tumor necrosis factor-α (TNF-α) treatment, as well as the development of new EA-RA.

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MATERIALS AND METHODS

EA-RA was defined as known manifestations of RA. These were assessed individually (for each patient) by a rheumatologist in collaboration with respective teams (chest physicians, dermatologists, renal physicians, surgeons) and found to be in the context of RA based on clinical judgment and investigations (computed tomography for lung disease, skin biopsy, and antineutrophil cytoplasmic antibodies for cutaneous vasculitis, urine dipstick, and serum creatinine for renal disease).

A number of 152 patients (86.7% women) with an established diagnosis of RA were included, from a database of 500 patients receiving biologic agents at the time of our study. The catchment area of the hospital is about 1.9 million people. All patients were being followed up in the Rheumatology Department at Charing Cross Hospital (London, UK) at the time of our study, and they had received anti-TNF-α therapy [infliximab (IFX), etanercept (ETN), adalimumab (ADA)], which was initiated between 2000 and 2011.

The hospital notes were requested in alphabetical order from the hospital rheumatology biologics database. The aim was to enroll the first 50 patients on the list from each group (IFX, ETN, ADA). However, because there were not enough patients receiving IFX and there were a significant number of patients who received sequential anti-TNF-α agents, this was not entirely possible.

The followup period ended at death, migration from the area, loss to followup, or April 2012.

As golimumab and certolizumab pegol were not used routinely at Charing Cross Hospital, patients receiving either of these anti-TNF-α agents were excluded. Patients who had information missing in paper or electronic notes were excluded.

Therefore, our study was not based on a defined population of patients with RA, but on a clinical convenience sample.

The following were documented for each patient: demographics, relevant comorbidities, age at RA onset, antibody status, conventional disease-modifying antirheumatic drugs and duration, anti-TNF start date, stop date, and duration; and mean Disease Activity Score at 28 joints (DAS28) while taking anti-TNF agents (Table 1).

Table 1. Baseline demographics, disease characteristics, and anti-TNF-α treatment for the full analysis set and subgroups of patients. Percentage is calculated from the number of patients with a clear evidence of positivity/negativity.

	All	No EA-RA	EA-RA Overall	EA-RA New
Demographics				
Patients, n	152	110	42	22
Female, n (%)	131 (86.7)	94 (62.2)	37 (88.1)	17 (77.3)
Mean age, yrs	56.4	53.7	63.6	63.1
Disease characteristics				
Age at RA onset, mean, yrs	39.3	37.4	44.3	44.9
Disease evolution period, mean, yrs	20	16	20.3	18.4
Disease evolution period before starting anti-TNF, mean, yrs	12.1	9.6	12.9	9.9
DAS28 value during anti-TNF, mean	3.86	3.25	3.63	3.17
Immunology				
Anti-CCP-positive, n (%)*	79 (82.3)	59 (79.7)	20 (90.9)	10 (100)
RF-positive, n (%)*	116 (81.7)	80 (77.6)	36 (92.3)	20 (95.2)
Medication				
Infliximab, n	9	6	3	1
Adalimumab, n	47	34	13	6
Etanercept, n	54	40	14	7
More than 1 anti-TNF-α, n	42	30	12	8
Anti-TNF-α monotherapy†, n	6	6	0	0

*In some of the cases, anti-CCP antibodies/RF could not be found, either in the notes or on the electronic system. The percentage is calculated from the number of patients with known antibody status. †Not in combination with a disease-modifying agent. EA-RA: extraarticular manifestations of rheumatoid arthritis; anti-TNF: antitumor necrosis factor; anti-CCP: anticyclic citrullinated peptide antibodies; RF: rheumatoid factor; DAS28: 28-joint Disease Activity Score.

RESULTS

Nine patients received IFX (5.9%), 54 received ETN (35.5%), 47 received ADA (30.9%), and 42 patients (27.7%) had received sequential anti-TNF-α therapies (Table 1). A number of 110 patients (72.8%) never had EA-RA, whereas 42 patients (27.2%) had EA-RA before or after commencing anti-TNF-α therapy.

In 22 cases (14.5%), a new EA-RA developed after starting anti-TNF-α agents (8 cases of lung disease, 11 cases of subcutaneous rheumatoid nodules, and 3 cases of cutaneous vasculitis). In 5 cases, there was clear evidence of progression of preexisting EA-RA (2 lung disease, 3 nodules). Regression was found in 4 cases of nodular RA. Renal disease (chronic kidney disease and proteinuria) was found in just 1 case, and it had a stable evolution throughout the whole period of anti-TNF-α treatment. In this particular case, the multidisciplinary team formed of rheumatologists and renal physicians could not find a definite cause for the chronic kidney disease. Possible explanations were RA-related, light-chain amyloidosis, methotrexate therapy, or penicillamine therapy in the past. In the rest of the cases, the evolution of EA-RA remains unclear (Figure 1).

The incidence rate of new onset of EA-RA was 7.5 cases per 1000 person-years.

No cases of Felty syndrome, scleritis, pericarditis, or pleuritis were found in our study.

DISCUSSION

In our study, EA-RA was present in a higher percentage compared to the prevalence of the EA-RA previously reported in studies (8-12%)[1,2,3,4]. A possible explanation for this could be that patients who are being followed up in secondary care and treated with TNF-α blockers have a more severe form of disease.

A retrospective Swedish review (July 1997–December 2004) found that the incidence of severe EA-RA (classified according to predefined criteria) was 0.49/100 patient-year in patients treated with anti-TNF-α (1.16/100 in patients not treated with TNF-α inhibitors). This is lower than we found in our study; however, we did not use preestablished criteria for EA-RA and therefore the comparability with other studies is limited[7].

In our study, only women developed lung disease, renal impairment, or vasculitis, but this could be attributable to the higher prevalence of RA among the female population rather than a higher risk for EA-RA in women. It is also worth mentioning that the average age at disease onset was low in all groups, which might be one of the explanations for the higher percentage of EA-RA in our study compared to literature.

The percentage of seropositivity in the non–EA-RA group (for both RF and anticitrullinated protein antibodies) was less than 80%, compared to more than 90% in the EA-RA. This confirms a well-known association between EA-RA and the presence of RF[6].

There were no significant differences in the 2 groups regarding smoking: 65.4% patients with EA-RA and 65.9% patients without EA-RA were smokers/ex-smokers.

Out of the 22 cases of new onset EA-RA, only 6 patients were in remission during the anti-TNF-α treatment period

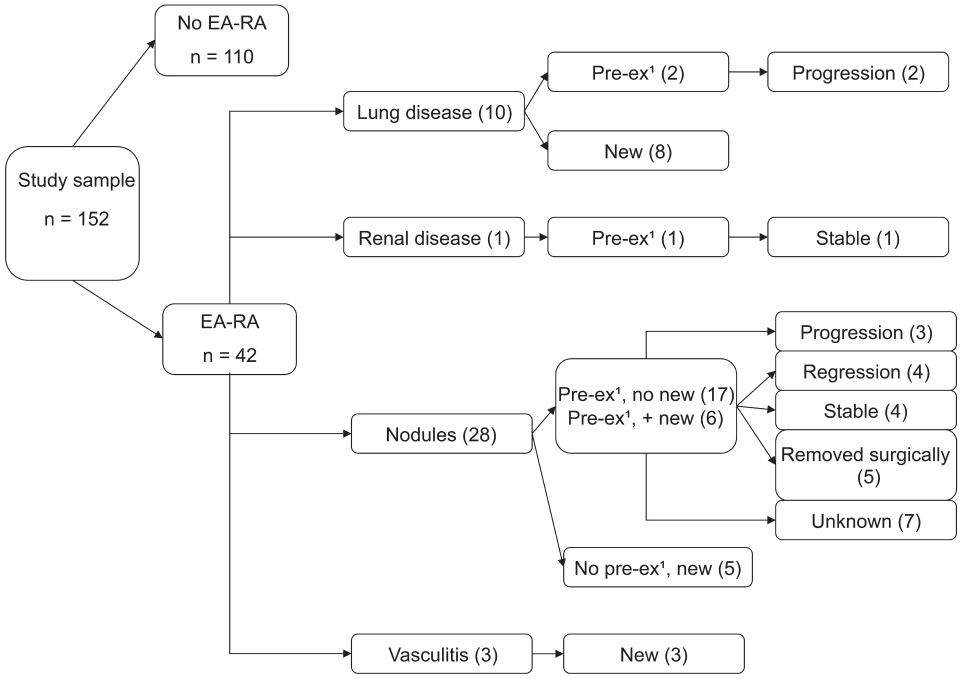

Figure 1. Evolution of EA-RA on anti-TNF-α treatment. EA-RA: extraarticular manifestations of rheumatoid arthritis; TNF-α: anti-tumor necrosis factor-α.

(2 cases of new lung disease, 4 cases of nodule development). Therefore, in these cases, the development of EA-RA cannot be associated with the disease activity; an alternative explanation is that anti-TNF-α treatment was associated with new EA-RA.

Out of 5 cases of progression of EA-RA on anti-TNF-α, only 1 patient who developed lung disease was in remission. The other 4 patients (of which 1 developed lung disease, 3 developed nodules) had DAS28 consistent with moderately/highly active disease[8]. Therefore, in these 4 cases, the progression is more likely to be associated with an active disease rather than related to anti-TNF-α treatment.

A major limitation of our study is not having a control group of patients with RA not treated with anti-TNF-α. Another limitation of our study is the use of mean DAS28 as opposed to stable remission (DAS28 < 2.6 at all times), stable low disease activity (DAS28 < 3.2 at all times), and active/fluctuating disease (DAS28 > 3.2 at least once), which would have been a more accurate and helpful method in analyzing data. The mean values for DAS28 during anti-TNF treatment include data points derived after the onset of extraarticular manifestations in the new cases; however, the number of patients treated for EA-RA in our study was small (only 3 patients were treated with steroids for EA-RA).

Flares and EA-RA are still present in patients treated with anti-TNF-α. In some cases, this is attributable to treatment failure because of high disease activity. In other cases, where patients had a DAS28 score indicating remission (< 2.6), the development of EA-RA may be either associated with the use of anti-TNF-α or with the residual, clinically relevant inflammation despite having a DAS28 score < 2.6. Regardless of the cause, development of new severe EA-RA is rare in patients receiving anti-TNF therapy (7.2%).

It is possible that other confounding factors are responsible for our findings. We propose that further investigation of this possible association is needed using appropriate methods of control for confounders.

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