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Rheumatology 2019;58:1872–1873

doi:10.1093/rheumatology/kez147

Advance Access publication 27 April 2019

Can serum interleukin-17 and interleukin-10 levels predict response to biologic treatments in patients with rheumatoid arthritis?

Rheumatology key message

- IL-17 levels do not predict response/non-response to anti-TNF drugs.

SIR, The cytokine IL-17, subclassified into IL-17A, IL-17F and IL-17AF, has an important pro-inflammatory role, stimulating IL-1 and TNF production, IL-6 secretion and upregulation of RANK ligand, which promotes bone erosion [1]. In contrast, the cytokine IL-10 acts by blocking the secretion of pro-inflammatory cytokines [2]. We hypothesized that patients whose disease activity is not adequately controlled by anti-TNF therapies in RA may have IL-17-driven disease and that lower IL-10 levels may play a permissive role. Our objective was to determine whether pretreatment or 3 month IL-17/IL-10 concentrations correlate with treatment response to anti-TNF drugs by 6 months of treatment.

We collected data as part of the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGS). Ethical approval was obtained for the BRAGGS study via a local ethics committee. Written informed patient consent was obtained at the time of recruitment to the study. Patients were followed up at pretreatment (baseline) and 3, 6 and 12 months, with blood samples, questionnaires and clinical data obtained. RA patients were eligible for inclusion if they were commencing adalimumab or etanercept. Patients were designated as good or poor EULAR responders at 6 months. Cytokine levels were measured using the Erenna Immunoassay system (Singulex, Alameda, CA, USA), which utilizes single molecule counting technology for high sensitivity. The samples and standards were prepared manually (including any dilutions necessary), which were then loaded onto a Biomek FX^P liquid handler robotic platform (Beckman Coulter, Brea, CA, USA) to perform the assay as per the manufacturer's instructions. The Wilcoxon rank sum test was used to compare IL levels at pretreatment and 3 months according to the EULAR classification by 6 months. Logistic regression analysis was carried out adjusting for gender, 28-joint DAS (DAS-28), and baseline Disease Modifying Anti-Rheumatic Drug (DMARD), Non-Steroidal Anti-Inflammatory Drug (NSAID) or oral steroid use.

A total of 152 patients were included, with 80 patients treated with adalimumab and 72 with etanercept. Of these, 108 patients were female and 42 were male. There was no statistically significant difference between mean IL-17A, IL-17AF, IL-17F and IL-10 levels at baseline and at the 3 month follow-up (Table 1). Analysis of IL-17:IL-10 ratios at these time points also failed to yield significant results. For IL-17A, those patients classified as good responders by 6 months demonstrated an increase in mean serum levels of IL-17A from 1.06 pg/ml at baseline to 1.23 pg/ml at 3 months. This came close to statistical significance ($P = 0.07$). Further analysis was carried out by drug group and also a subgroup analysis by drug group linked to responder status for all of the above cytokines. No statistically significant results were obtained. Adjusting for gender, DAS-28 score and baseline DMARD, NSAID or oral steroid use did not alter our findings.

TABLE 1 Mean IL levels at pretreatment and 3 months

Interleukin levels, pg/ml	All patients (<i>n</i> = 152)	P-value	Good responders (<i>n</i> = 86)	P-value	Poor responders (<i>n</i> = 66)	P-value
Baseline IL-17A	1.16	–	1.06	–	1.29	–
3 month IL-17A	1.21	0.76	1.23	0.07	1.19	0.49
Baseline IL-17AF	21.51	–	16.40	–	28.32	–
3 month IL-17AF	30.98	0.57	21.89	0.58	42.43	0.81
Baseline IL-17F	1.97	–	2.50	–	1.28	–
3 month IL-17F	1.59	0.66	1.41	0.89	1.81	0.42
Baseline IL-10	9.26	–	8.41	–	10.38	–
3 month IL-10	10.52	0.93	11.49	0.59	9.33	0.42

We found no evidence to support a correlation between pretreatment and 3 month IL-17F, IL-17AF and IL-10 concentrations. While an increase in IL-17A serum levels between baseline and 3 months showed a trend towards an association with a good EULAR response status by 6 months, the 3 month level was similar to that seen in poor responders, suggesting that the finding may have occurred by chance; larger sample sizes are required to confirm this.

Acknowledgements

AB received a National Institute for Health Research Senior Investigator award.

Funding: This work was funded by the Manchester Molecular Pathology Node, MMPathic (grant MR/N00583X/1) and supported by the National Institute for Health Research Manchester Biomedical Research Centre and Arthritis Research UK (grant 21754).

Disclosure statement: The authors have declared no conflicts of interest.

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Accepted 22 March 2019

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Rheumatology 2019;58:1873–1875

doi:10.1093/rheumatology/kez167

Advance Access publication 28 April 2019

Thrombotic microangiopathy associated with anti-neutrophil cytoplasmic antibody-associated vasculitis: a French nationwide retrospective case-control study and literature review

Rheumatology key message

- Thrombotic microangiopathy should be suspected in ANCA-associated vasculitis with severe organ failure, thrombocytopenia and high lactate dehydrogenase levels.

SIR, Thrombotic microangiopathy (TMA) is characterized by endothelial cell injury, intravascular platelet-fibrin thrombi and vascular damage [1]. ANCA-associated vasculitis (AAV) is characterized by inflammatory changes of small- to medium-sized blood vessels. Although kidney biopsies of patients with renal vasculitis demonstrate the presence of histological features of TMA [2], thrombotic thrombocytopenic purpura (TTP) in AAV is exceptional [3, 4].

From the French thrombotic microangiopathies reference centre registry, we collected all cases of TMA associated with vasculitis with time between the two diagnoses <5 years. We searched for case reports in MEDLINE via PubMed, Web of Science and congress abstracts from January 2005 to August 2017 by using ‘thrombotic thrombocytopenic purpura’, ‘microangiopathy’, ‘thrombotic microangiopathy’, ‘vasculitis’, ‘ANCA-positive vasculitis’, ‘ANCA-associated vasculitis’, ‘granulomatosis with polyangiitis’, ‘microscopic polyangiitis’, ‘eosinophilic granulomatosis with polyangiitis’ and ‘renal-limited vasculitis’ [3–11].

Because our case-series and literature data were mostly about microscopic polyangiitis (MPA), we used data for a control group of patients with MPA without TMA from the Saint Antoine and Montfermeil hospitals registry of patients with AAV. From 1587 cases recorded in the French nationwide registry of TMA from September 1995 to September 2015, we found 8 with vasculitis [median age 45 (range 21–76) years; female/male ratio 0.75]. The vasculitis was cryoglobulinemic vasculitis associated with Sjögren’s syndrome ($n=1$), leucocytoclastic vasculitis ($n=2$), MPA ($n=2$), granulomatosis with polyangiitis ($n=1$) and unclassified ($n=2$). Thus, the prevalence of vasculitis was 5/1000 cases of TMA in our study. The clinical features at vasculitis diagnosis are summarized in Table 1. The BVAS [median (range)] at diagnosis was 16 (9–28) and Five Factor Score was 1 (0–2). Steroids were used in five (63%) cases, combined with immunosuppressive drugs in six (75%): CYC, rituximab and HCQ, two cases each. The median time between the diagnosis of vasculitis and TMA was 9 (range 0–51) months (supplementary Table S1, available at *Rheumatology* online). Both diseases occurred concomitantly in two cases, and vasculitis preceded TMA in six cases. At the time of TMA, three patients had active vasculitis. ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1