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LETTER

Targeting type I interferon (IFN) signalling in patients with RA with a high type I IFN gene signature

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A peripheral blood type I interferon (IFN) gene signature can be found in approximately 50% of patients with rheumatoid arthritis (RA),[1] suggesting that activation of the type I IFN system contributes to RA pathogenesis within this subset of patients. Therefore, the question arises whether blocking the type I IFN response, especially in patients with a high type I IFN gene signature, would be an effective treatment approach for RA. To address this question and to estimate the potential for the future planning of a larger study, we conducted a randomised, double-blind, placebo-controlled multicentre pilot trial, in which we planned to include 24 patients with RA with active disease and a high type I IFN gene signature to receive the type I IFN receptor blocking antibody anifrolumab[2] or placebo intravenously every 4 weeks for a total of six doses (trial registration number NCT03435601; start of study: December 2017; end of study: November 2020). Inclusion criteria, among others, were current treatment with a conventional synthetic disease-modifying antirheumatic drug (DMARD) and failure to clinically respond to at least one Tumor necrosis factor alpha (TNF)-inhibitor but no more than a total of three biological DMARDs; patients had to have moderately to highly active disease. To identify patients with RA with a high IFN signature, we applied a four-gene (IFI27, IFI44, IFI44L, RSAD2) quantitative PCR-based test (QIAGEN) using RNA extracted from whole blood collected in PAXgene Blood RNA tubes (PreAnalytiX).[3] Recruitment turned out difficult not least because of the evolution of the COVID-19 pandemic and, therefore, the study was prematurely stopped. Here, we report on the overall results of this pilot trial.

Eighteen screening visits in 16 patients were performed (2 patients were screened twice). A negative IFN signature was the most common reason (n=9) for ineligibility. Among the seven randomised patients, four were assigned to receive anifrolumab and three placebo. Disposition of study patients, screening visit and baseline demographics and disease characteristics are shown in figure 1A, online supplemental figure 1 and online supplemental table 1. Three patients treated with anifrolumab prematurely discontinued the study: one due to lack of efficacy, one due to hypersensitivity reaction (skin rash) shortly after the second infusion and one because of infection triggered exacerbation of bronchial asthma 3 weeks after the first anifrolumab infusion. Two participants in the placebo group discontinued due to insufficient therapeutic response. Thus, only one patient in each treatment group completed the study. Achieving an American College of Rheumatology (ACR) response of ≥20% after 24 weeks of treatment was the primary endpoint in this study. One patient in the anifrolumab, but none in the placebo group achieved an ACR 20 response at 24 weeks (figure 1B, non-responder imputation). Changes in disease activity for each patient over time are presented in figure 1C,D and online supplemental tables 2 and 3. Improvement in RA disease activity, especially within the first 4 weeks, was seen in all patients treated with anifrolumab. In total, 12 adverse events (AEs) in 6 patients were reported (online supplemental table 4). Most AEs were mild. Two serious AEs were reported: one in the anifrolumab group (infection triggered exacerbation of bronchial asthma) and one in the placebo group (arterial thrombosis shortly after infusions were discontinued due

A.

Characteristics	All (n=7)	Placebo (n=3)	Anifrolumab (n=4)
Female sex, no. (%)	5 (71%)	2 (67%)	3 (75%)
Age, year	53.4 (37-74)	60.3 (53-74)	48.3 (37-59)
DAS28	6.1 (4.5-7.1)	5.8 (4.5-6.6)	6.4 (6.1-7.1)
CDAI	37.8 (17.7-62.3)	30.2 (17.7-42)	43.6 (34-62.3)
SDAI	39.9 (17.9-69.9)	30.8 (17.9-42.3)	46.7 (34.6-69.9)
CRP, mg/dl	2.1 (0.2-7.6)	0.6 (0.2-1.4)	3.1 (0.6-7.6)
ESR, mm/hour	33 (11-52)	24.3 (11-37)	41.7 (30-52)
Methotrexate, no.	5	1	4
Leflunomid, no.	2	2	0
Previous bDMARDS, no.			
1	2	1	1
2	3	2	1
≥3	2	0	2

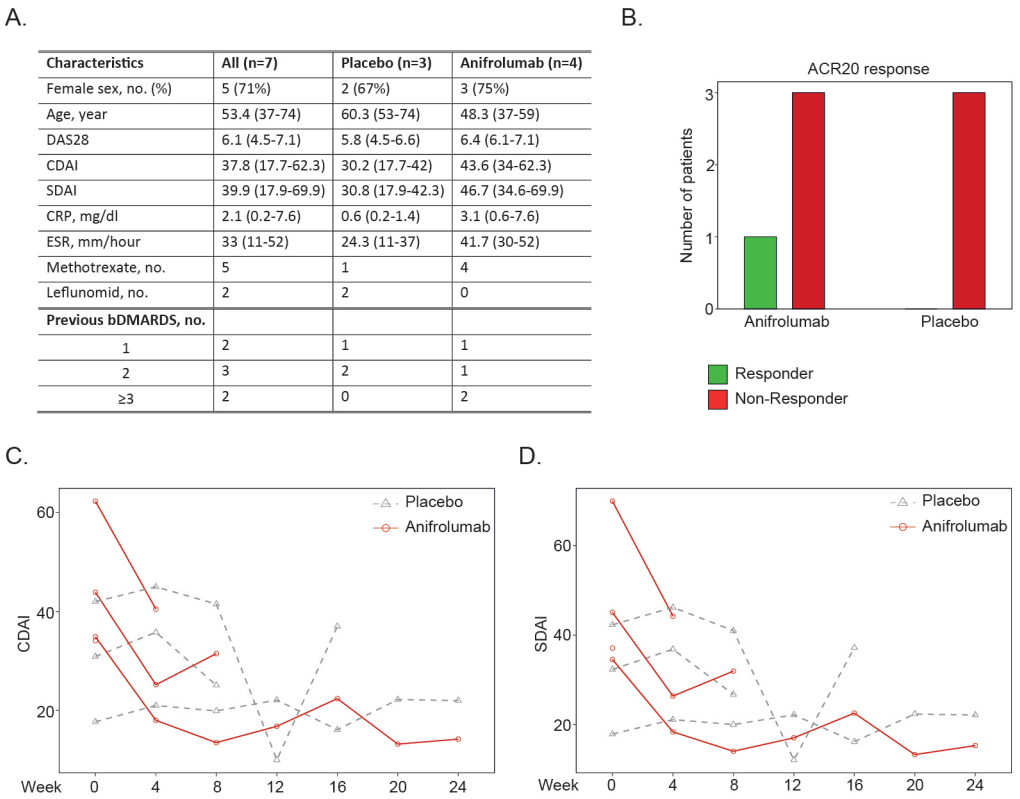

Figure 1 (A) Demographic and clinical characteristics of study participants at baseline. Mean (minimum-maximum value). (B) ACR20 response at week 24 (non-responder imputation). (C.) Trend lines for changes in CDAI. (D.) Trend lines for changes in SDAI. (C and D) Note, that for one patient only baseline values are shown, since this patient prematurely left the trial due to infection triggered exacerbation of asthma. The strong decrease of CDAI and SDAI of one of the patients in the placebo group at week 12 was due to a transient substantial reduction in the tender joint count. ACR, American College of RHeumatology; bDMARD, biological Disease-modifying antirheumatic drugs; CDAI, clinical disease activity index; CRP, C reactive protein; DAS28, Disease Activity Score 28; ESR, erythrocyte sedimentation rate; no., number; SDAI, Simplified Disease Activity Index.

to lack of efficacy). There were no cases of visceral or disseminated herpes zoster, malignancies or other AEs of special interest, such as opportunistic infections.

Overall, our data support previous reports showing that a type I IFN gene signature can be found in approximately half of patients with RA. Safety profile of anifrolumab in this study was comparable to already published trials in Systemic Lupus Erythematosus (SLE).[4 5] Although clinical efficacy was observed in patients treated with anifrolumab no conclusions regarding the efficacy can be drawn due to the limited number of patients who completed this trial.

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