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CLINICAL SCIENCE

Association of rheumatoid factor, anti-citrullinated protein antibodies and shared epitope with clinical response to initial treatment in patients with early rheumatoid arthritis: data from a randomised controlled trial

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ABSTRACT

Objectives To investigate whether rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPAs) and shared epitope (SE) allele-related genetic markers associate with treatment response to abatacept, certolizumab pegol or tocilizumab versus active conventional treatment (ACT).

Methods Patients with treatment-naïve early rheumatoid arthritis were randomised in the NORD-STAR trial to ACT, certolizumab pegol, abatacept or tocilizumab, all with methotrexate. Centralised laboratory analyses for ACPA, RF and SE were performed. Clinical Disease Activity Index remission was analysed longitudinally with logistic generalised estimating equations. Differences in treatment effect across RF, ACPA and SE subgroups were assessed with interaction terms at 24 and 48 weeks, adjusted for sex, country, age, body mass index, Disease Activity Score of 28 joints based on C-reactive protein and smoking.

Results In total, 778 patients were included. At 24 weeks, abatacept treatment showed a better response than ACT in the RF and/or ACPA-positive subgroups, but this effect was not significantly different from the negative subgroups. By 48 weeks, abatacept treatment showed better response regardless of RF/ACPA status. No differences were found across RF, ACPA, SE allele, valine at amino acid position 11 or valine-arginine-alanine haplotype subgroups for any biological treatment at 48 weeks.

Conclusions Based on this randomised controlled trial, abatacept treatment was associated with a better response than ACT in the RF and/or ACPA-positive subgroup at 24 weeks, but this was no longer seen at 48 weeks; adding SE allele-related genetic markers did not strengthen the association. Moreover, ACPA, RF and SE allele-related genotypes were not, alone or in combination, associated with clinical responses of importance sufficiently strongly to warrant implementation in clinical practice.

Trial registration number EudraCT 2011-004720-35; ClinicalTrials.gov NCT01491815.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) serology are important components in rheumatoid arthritis diagnosis.

⇒ Previous studies have indicated that ACPA and/or RF positivity may selectively associate with a better response to abatacept treatment.

INTRODUCTION

Rheumatoid arthritis (RA) is a complex and heterogeneous disease associated with chronic joint inflammation. The classical subdivision of the disease has been made on the basis of the presence or absence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs).[1]

The development of ACPA-positive or RF-positive RA has been associated with the presence of HLA DRB1 shared epitope alleles.[1]

The most established environmental risk factor for the disease is cigarette smoking.[1] Interestingly, smoking has been shown to increase the risk of developing RA in the subset of patients positive for RF or ACPA carrying shared epitope genes and to have a very minor effect on the antibody-negative subset of patients.[1–4]

Previous research has indicated that the response to targeted therapies with different mechanisms of action may vary based on the patient's underlying ACPA or RF status in biological-naïve patients[5 6] as well as in real-world settings.[7] Several studies have shown that ACPA and/or RF positivity may selectively associate with a better response to abatacept treatment.[8 9] Moreover, a notable improvement in disease activity among ACPA and RF positive patients receiving abatacept treatment was observed particularly in individuals positive for the shared epitope (SE) allele, a trend not observed

WHAT THIS STUDY ADDS

⇒ The addition of shared epitope allele status or related genetic markers, valine at amino acid position 11 (Val11) or valine-arginine-alanine (VRA) haplotype, to RF and ACPA serology did not strengthen the association.

⇒ We found no evidence of heterogeneity of treatment effect based on RF, ACPA, shared epitope allele, Val11 or VRA subgroups in any of the three biological treatment groups when compared with active conventional treatment at 48 weeks.

⇒ Abatacept treatment was associated with a better response than active conventional treatment in the RF and/or ACPA positive subgroup at 24 weeks. However, because the interaction terms were not statistically significant, the effect observed in the positive subgroup was not significantly different from the effect in the negative subgroup. By 48 weeks, abatacept treatment showed a better response, regardless of RF/ACPA status.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Autoantibody positive patients, in whom B cells might play a major part in rheumatoid arthritis disease activity, experienced earlier disease suppression with abatacept treatment when compared with active conventional treatment. However, the relevance of the baseline autoantibody profile appears to diminish over time.

with the tumour necrosis factor (TNF) inhibitor adalimumab treatment.[10]

In contrast, other studies suggested that more specific genetic markers related to SE allele or valine at amino acid position 11 of HLA-DRB1 (outside the SE) could be in association with treatment response in RA.[11 12]

However, the advantages (or disadvantages) of treating treatment-naïve patients based on their serological profile and SE genotype have not been evaluated in head-to-head randomised controlled trials that allow a direct comparison of several biological treatments with different mechanisms of action, using active conventional treatment as the reference.

The NORD-STAR trial, an investigator-initiated international randomised controlled clinical trial, involved 812 patients with treatment-naive RA.[13–15] These individuals were randomly assigned to four treatment groups and received either active conventional treatment (methotrexate combined with either oral glucocorticoids or with sulfasalazine plus hydroxychloroquine plus intra-articular glucocorticoids), methotrexate plus certolizumab pegol (tumour necrosis factor inhibitor), methotrexate plus abatacept (T-cell co-stimulation blocker) or methotrexate plus tocilizumab (interleukin 6 inhibitor).

In this substudy of the NORD-STAR randomised controlled trial, we aimed to investigate whether the presence of ACPA, RF and SE alleles associated with treatment response with abatacept as well as with certolizumab pegol, or tocilizumab versus active conventional treatment in early RA.

METHODS

Study design and participants

The NORD-STAR trial was a phase 4, multicentre, investigator-initiated, open-label, assessor-blinded, randomised controlled trial of early RA, conducted in Sweden, Denmark, Norway, Finland, the Netherlands and Iceland that enrolled 812 patients. Newly diagnosed patients, fulfilling the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for RA, aged 18 or older, naive to disease-modifying antirheumatic drugs, with symptom duration less than 24 months, with moderate-to-severe Disease Activity Score of 28 joints (DAS28-C-reactive protein (CRP)>3.2), and with ACPA, RF positivity or increased CRP (≥10 mg/L), or a combination of the above, were eligible for enrolment (online supplemental file 2). The primary NORD-STAR analysis population was the intention-to-treat population, which included all patients who entered the study, except 17 Finnish patients, for whom allocated treatment (tocilizumab) was not available. All patients from the primary NORD-STAR analysis population[13 14] with available blood samples were included in this substudy.

Randomisation

In the NORD-STAR trial participants were assessed and randomly assigned in a 1:1:1:1 ratio stratified by country, sex and ACPA status into one of the following treatment groups:

- Treatment group 1 received active conventional treatment either:
  - 1A (Sweden, Norway, Netherlands and Iceland) methotrexate plus oral prednisolone (tapered from 20 mg to 5 mg per day within 9 weeks and discontinued at week 36) or
  - 1B (Denmark, and Finland) methotrexate plus sulfasalazine (2 g per day), plus hydroxychloroquine (35 mg/kg per week or 200 mg per day), plus intra-articular glucocorticoids in the swollen joint (triamcinolone hexacetonide (or equivalent) injections; maximally four joints and 80 mg per visit).
- Treatment group 2 received methotrexate plus certolizumab pegol (200 mg subcutaneously administered every other week (loading dose 400 mg at 0, 2 and 4 weeks).
- Treatment group 3 received methotrexate plus abatacept (125 mg subcutaneously administered every week).
- Treatment group 4 received methotrexate plus tocilizumab (8 mg/kg intravenously administered every 4 weeks or 162 mg subcutaneously administered every week).

All patients started with concomitant methotrexate on day 1 (initially 10–15 mg orally administered) which was given in a step-up schedule aiming to achieve the target weekly dose of 25 mg by week 4. Investigators were allowed to deviate from the prescribed methotrexate strategy when clinically justified.[15]

Oral steroids were allowed only in patients receiving prednisolone in treatment group 1A. Intra-articular glucocorticoid injections were administered in all treatment groups when clinically indicated (or for group 1B, whenever a swollen joint was detected at a visit). In each treatment group, the use of intra-articular glucocorticoids was restricted during weeks 20–24 and 44–48 to minimise their impact on efficacy outcomes at 24 and 48 weeks.[13–15]

Procedures

Laboratory measures

Serum samples were obtained at baseline visit and stored at −80°C until analysis.

ACPA and RF were measured using the EliA (IgG and IgM) methods on a Phadia 250 instrument from Thermo Fisher Scientific (Freiburg, Germany https://www.thermofisher.com/phadia/wo/en/our-solutions/elia-autoimmunity-solutions/

rheumatoid-arthritis.html) according to suppliers' instructions. ACPA positivity was defined as a concentration of greater than 10 U/mL and RF positivity as a concentration of greater than 5 IU/mL.

DNA extraction from peripheral blood was performed either by salting out method or with Quick-DNA Midiprep Plus Kit (Zymo Research, Cat No. D4075) and DNA concentration was assessed by optical density on QIAxpert (QIAGEN). Participants were genotyped using Illumina GSA and HLA class 2 alleles were imputed by SNP2HLA algorithm.[16] The presence of HLA-DRB1 alleles was classified as SE-positive (one or two SE alleles) or SE-negative (no SE alleles). Within this study the SE alleles for HLA-DRB1 are those from allelic family HLA-DRB1*01 (with the exclusion of *01:03), allelic family HLA-DRB1*04 (with the exclusion of *04:02, *04:03, *04:06), allelic family HLA-DRB1*10 and HLA-DRB1*14:02.

Outcomes

Clinical Disease Activity Index remission (CDAI≤2.8) at 24 and 48 weeks was used as the primary outcome for this substudy.[17] Secondary efficacy outcomes were (1) DAS-28-CRP remission (DAS28-CRP<2.6),[18] and (2) a 70% or greater response in ACR criteria (ACR70)[19] response at 24 and 48 weeks.

Statistical analysis

The three outcomes were analysed longitudinally (4, 8, 12, 16, 24, 32, 40 and 48 weeks) with logistic generalised estimating equations (GEE) analysis. To analyse differences in treatment response between particular subgroups, based on RF, ACPA and SE allele status individually and in combinations at 24 and 48 weeks, the model included treatment (represented by three dummy variables), time (represented by seven dummy variables), particular subgroup (positive vs negative), all two-way interaction and three-way interaction (ie, between treatment, time and the particular subgroup). In the analysis, time was treated as a categorical variable. With the GEE analysis, we obtained point estimates and 95% CIs for the subgroup differences in treatment effects at 24 and 48 weeks. By changing the reference category for the categorical variables, we obtained point estimates for particular subgroup and time point. Analyses were adjusted for sex, country, age, body mass index, DAS28-CRP and smoking status at baseline. Given that the NORD-STAR trial was designed to detect differences between treatment groups, a p value<0.1 for interactions was considered statistically significant to determine whether the treatment effects differ according to subgroups. Treatment effects for the biological treatments are presented as the adjusted average marginal differences in CDAI remission rates in comparison to active conventional treatment.

Statistical analyses were performed using Stata (V.18) and SPSS statistical software (V.28). GraphPad Prism V.10 was used for the figures. The NORD-STAR trial is registered with EudraCT and ClinicalTrials.gov.

RESULTS

Between December 2012 and December 2018, a total of 812 patients underwent randomisation in the NORD-STAR trial. The primary NORD-STAR analysis population was the intention-to-treat population, defined as all randomised patients except 17 Finnish patients, for whom allocated treatment (tocilizumab) was not available.[13 14]

Of the 795 primary NORD-STAR analysis population patients, serum samples were available for 770 patients and whole blood samples for 703 patients. A total of 778 patients with centrally analysed serum and/or whole blood samples were included in this substudy (figure 1). Overall, 604/770 (78%) were RF positive, 633/770 (82%) were ACPA positive, 554/703 (79%) were SE allele positive, 676/770 (88%) had seropositive RA and 431/695 (62%) were positive for all three biomarkers. Patient characteristics stratified by treatment group are shown in table 1.

In general, seronegative (defined by the absence of RF and ACPA) patients exhibited higher disease activity compared with seropositive (positive for RF and/or ACPA) counterpart across all treatment groups at baseline. Details are shown in the online supplemental table S1, S2.

Out of 148 SE allele-negative patient, 86 (58%) were positive for ACPA and 93 (63%) were positive for RF.

Figure 2 shows the adjusted probabilities of CDAI remission across subgroups, based on RF, ACPA and SE status individually and in combination, for each of the four treatment groups at 24 and 48 weeks. We investigated the treatment response, using active conventional treatment as the reference for the three biological treatment. To determine whether the associations differed across subgroups (based on RF, ACPA and SE allele status individually or in combination), an interaction term was added to the GEE model. Table 2 shows the adjusted marginal differences in CDAI remission rates between active conventional treatment and each of the three biological treatments. Interaction p values indicate whether the treatment effect is different across subgroups between active conventional treatment versus each of the three biological treatments.

Abatacept treatment was associated with a better response than active conventional treatment (ACT) in the RF and/or ACPA-positive subgroup at 24 weeks. However, because the interaction terms were not statistically significant, the effect observed in the positive subgroup was not significantly different from the effect in the negative subgroup. By 48 weeks, abatacept treatment showed a better response than ACT regardless of RF/ACPA status. On the contrary, ACPA and/or RF-negative patients seem to show an enhanced response with certolizumab pegol compared with ACT at 24 weeks; however, this was a non-significant trend. An additional improvement was observed with certolizumab pegol and tocilizumab treatments for both ACPA and/or RF positive and negative patients at 48 weeks.

When we analysed CDAI remission rates based on participant's baseline RF, ACPA and SE status alone or in combination, the only significant interaction for CDAI remission was found with tocilizumab treatment, suggesting that triple-positive patients had a less favourable effect than patients with other combinations when compared with active conventional treatment at 24 weeks. However, the interaction was no longer significant at 48 weeks.

Thus, at 48 weeks, we found no evidence of heterogeneity of treatment effect based on RF, ACPA and SE status individually or in combination in any of the biological treatment groups when compared with active conventional treatment.

Results of DAS28-CRP remission rates and ACR70 response rates are presented in the online supplemental tables S3, S4 and figures S1, S2. There were no significant interactions when analysing the data with DAS28-CRP remission criteria. According to ACR70 response criteria, triple-positive patients with the tocilizumab treatment showed a significantly poorer treatment effect than other combinations at 24 weeks but not at 48 weeks when compared with active conventional treatment. An additional significant interaction observed in the tocilizumab treatment suggested that seropositive patients had a better response compared with seronegative patients at 48 weeks.

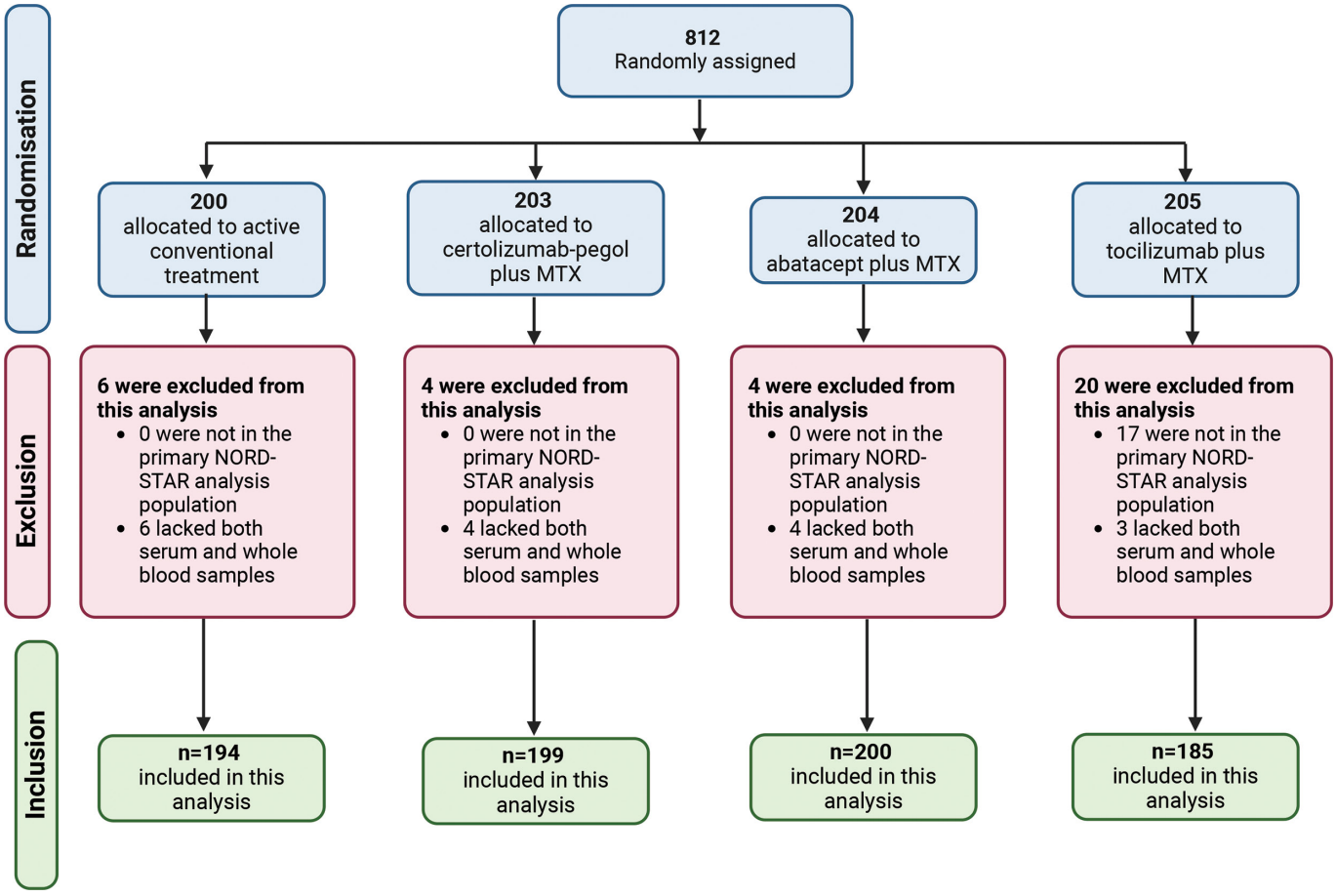

Figure 1 Flow diagram of included patients. MTX, methotrexate.

We did not observe any significant associations between HLA-DRB1 valine at amino acid position 11 or valine-arginine-alanine haplotype and CDAI remission individually, and in combination with RF and ACPA positivity at 48 weeks (online supplemental table 5 and figure S3).

No discernible patterns of association between baseline ACPA or RF titres and CDAI remission were observed (online supplemental figures S4, S5).

DISCUSSION

We investigated in a large investigator-initiated randomised controlled trial of early RA whether the presence of ACPA, RF and SE allele-related genetic markers either individually or in combination are associated with clinical response to initial treatment with abatacept, as well as with certolizumab pegol or tocilizumab using active conventional treatment as the reference at 24 and 48 weeks.

At baseline, seronegative patients were older, exhibited higher disease activity, had more tender and swollen joints and yet experienced a shorter delay from the onset of symptoms to RA diagnosis compared with seropositive patients.

Patients who were eligible for our study had received RA diagnosis according to the 2010 ACR/EULAR criteria.[20] While seronegative patients are often regarded as having a less destructive disease, these patients must have more clinical symptoms and inflammatory severity to compensate for the lack of serological markers and to be classified as having RA. An additional inclusion criterion that contributed to higher disease activity in seronegative patients was a CRP level of ≥10 mg/L, which was not a prerequisite for seropositive patients.[15]

We found that RF and ACPA positivity was associated with a better response to abatacept at 24 weeks compared with active conventional treatment, a trend not observed with certolizumab pegol and tocilizumab treatment. However, after 48 weeks of treatment, individuals receiving abatacept treatment, showed higher remission rates compared with those receiving active conventional treatment regardless of ACPA or RF status.

An earlier study examined pooled patient-level data from four early RA trials, demonstrating beneficial treatment effects of abatacept treatment for patients with a short disease duration (<1 year), moderate to high disease activity (DAS28-CRP≥3.2), as well as positivity for ACPA and RF compared with patients without these characteristics and comparator treatments (adalimumab plus methotrexate or methotrexate alone) at 24 weeks.[8] These findings were consistent with our 24 weeks results, although we had ACT as the comparator group; however, the previous study did not analyse the data at 48 weeks.

In an observation study of established RA, ACPA positive patients receiving abatacept showed a greater clinical response at 6 months compared with ACPA negative patients, demonstrating a differential treatment response from TNF inhibitors.[9] Similarly, in another observational study, seropositivity was associated with higher response rates for non-TNF inhibitors, especially for rituximab (B-cell inhibitor) and abatacept at 1-year visit, but not for TNF inhibitors.[7] A meta-analysis revealed a positive association between ACPA positivity and EULAR response with abatacept treatment but not with TNF inhibitor. However, high in-between study heterogeneity was observed across included abatacept studies, likely due to varying follow-up time points.[21] Another meta-analysis found that the

Table 1 Baseline characteristics of patients with early rheumatoid arthritis stratified by treatment group

	Active conventional treatment (n=194)*	Certolizumab pegol plus methotrexate (n=199)†	Abatacept plus methotrexate (n=200)‡	Tocilizumab plus methotrexate (n=185)§
Female	135/194 (70)	136/199 (68)	137/200 (69)	127/185 (69)
Age, years	54.6 (14.6)	55.3 (15.3)	54.9 (14.4)	52.4 (14.5)
Symptom duration, days	145 (87–229)	143 (86–255)	161 (86–264)	157 (94–256)
Time since diagnosis, days	6 (0–15)	6 (0–17)	8 (1–19)	8 (1–18)
Body mass index, kg/m^2	26.5 (5.4)	25.7 (4.9)	25.9 (4.8)	26.7 (5.0)
Smoking				
Current smoker	35/194 (18)	47/198 (24)	49/200 (25)	42/185 (23)
Former smoker	80/194 (41)	77/198 (39)	76/200 (38)	59/185 (32)
Non-smoker	79/194 (41)	74/198 (37)	75/200 (38)	84/185 (45)
RF positive¶	146/193 (76)	153/197 (78)	159/196 (81)	146/184 (79)
RF titres (IU/mL)	26 (6–79)	31 (6–82)	36 (9–96)	20 (6–96)
ACPA positive¶	157/193 (81)	160/197 (81)	163/196 (83)	153/184 (83)
ACPA titres (U/mL)	250 (43–625)	177 (28–600)	224 (39–700)	225 (36–688)
SE allele positive	143/179 (80)	135/177 (76)	146/179 (82)	130/168 (77)
Single SE allele positive	91/179 (51)	95/177 (54)	101/179 (56)	82/168 (49)
Double SE allele positive	52/179 (29)	40/177 (23)	45/179 (25)	48/168 (29)
Seropositive rheumatoid arthritis	168/193 (87)	171/197 (87)	171/196 (87)	166/184 (90)
Triple positive (RF, ACPA and SE)	111/178 (62)	102/175 (58)	117/175 (67)	101/167 (61)
Valine positive at amino acid position 11	113/179 (63)	109/177 (62)	121/179 (68)	113/168 (68)
VRA haplotype positive	37/179 (21)	43/177 (24)	40/179 (22)	38/168 (23)
Valine, RF and ACPA positive	87/178 (49)	83/175 (47)	97/175 (55)	89/167 (53)
VRA, RF and ACPA positive	30/178 (17)	34/175 (19)	32/175 (18)	31/167 (19)
CDAI score	28.5 (12.1)	27.7 (12.3)	28.3 (11.1)	26.4 (11.5)
DAS28-CRP**	5.1 (1.1)	5.0 (1.1)	5.0 (1.0)	4.9 (1.0)
Swollen joint count (66 joints)	11.2 (7.3)	11.1 (7.5)	10.7 (6.8)	9.6 (6.1)
Tender joint count (68 joints)	16.8 (11.4)	15.2 (10.4)	15.9 (10.7)	14.7 (10.1)
C-reactive protein, mg/L	12 (4–25)	12 (4–23)	10 (4–26)	10 (4–21)

Data are n/N (%), mean (SD) or median (IQR).
Seropositive rheumatoid arthritis=positive for ACPA, RF or both.
*Missing data as follows: n=1 for centrally analysed RF, n=1 for centrally analysed ACPA, n=15 for SE allele, valine and VRA haplotype, n=1 for centrally analysed serology status, n=16 for triple positive status, positivity for valine, RF and ACPA and positivity for VRA, RF and ACPA. n=2 for CDAI score, n=1 for C-reactive protein.
†Missing data as follows: n=1 for smoking, n=2 for centrally analysed RF, n=2 for centrally analysed ACPA, n=22 for SE allele, valine and VRA haplotype, n=2 for centrally analysed serology status, n=24 for triple positive status, positivity for valine, RF and ACPA and positivity for VRA, RF and ACPA, n=2 for CDAI score, n=1 for C-reactive protein.
‡Missing data as follows: n=1 for body mass index, n=4 for centrally analysed RF, n=4 for centrally analysed ACPA, n=21 for SE allele, valine and VRA haplotype, n=4 for centrally analysed serology status, n=25 for triple positive status, positivity for valine, RF and ACPA and positivity for VRA, RF and ACPA.
§Missing data as follows: n=1 for symptom duration, n=1 for body mass index, n=1 for centrally analysed RF, n=1 for centrally analysed ACPA, n=17 for SE allele, valine and VRA haplotype, n=1 for centrally analysed serology status, n=18 for triple positive status, positivity for valine, RF and ACPA and positivity for VRA, RF and ACPA, n=3 for CDAI score.
¶Serum sample was taken at week 2 for two patients.
**DAS28-CRP was replaced with DAS28-ESR for one patient.
ACPA, anti-citrullinated protein antibodies; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score of 28 joints, based on C-reactive protein; DAS28-ESR, Disease Activity Score of 28 joints, based on erythrocyte sedimentation rate; RF, rheumatoid factor; SE, shared epitope ; Triple positive, positive for RF, ACPA and shared epitope allele; VRA, valine-arginine-alanine (amino acids at positions 11, 71 and 74 of HLA-DRB1).

effect of biological treatment is generally comparable in patients with and without RF/ACPA, regardless of the drug's mechanism of action or patient population.[22]

In this current study, the CDAI remission rates of the active conventional treatment did not change much from 24 weeks to 48 weeks, even following the discontinuation of oral glucocorticoids treatment at week 36.[14] In contrast, the CDAI remission rates continued to increase in all three biological treatments between 24 weeks and 48 weeks irrespective of the ACPA or RF status.

The reason for the observed varying response at 24 weeks in seropositive and seronegative patients treated with abatacept treatment is not fully known but could be associated with abatacept's selective modulation of T-cell co-stimulation and subsequent autoantibody production through interaction with B cells.[5]

T follicular helper cells are known to provide help to B cells within lymphoid organs and peripheral helper T cells within inflamed tissues.[23] The proportions of programmed cell death-1 (PD-1) positive follicular T cells in blood have been shown to predict response to abatacept both, in early untreated RA[24] and in established RA.[25] The frequencies of T peripheral helper cells have been reported to be influenced by the patient's ACPA and/or RF status.[26 27] A broader autoantibody positivity may indicate a more active humoral autoimmunity,[28] wherein seropositive patients, in whom B cells may play a major part in RA disease activity, might experience earlier disease suppression following the disruption of T-cell and B-cell collaboration by abatacept.

At 48 weeks, we observed no heterogeneity in treatment effects across subgroups in any of the biological treatment groups when compared with active conventional treatment. One possible explanation for this could be that conventionally defined seronegative RA may not be a 'true' seronegative subset of the disease. A prior study has shown that ACPA fine-specificities and IgA/IgG RF can be detected in a substantial proportion of

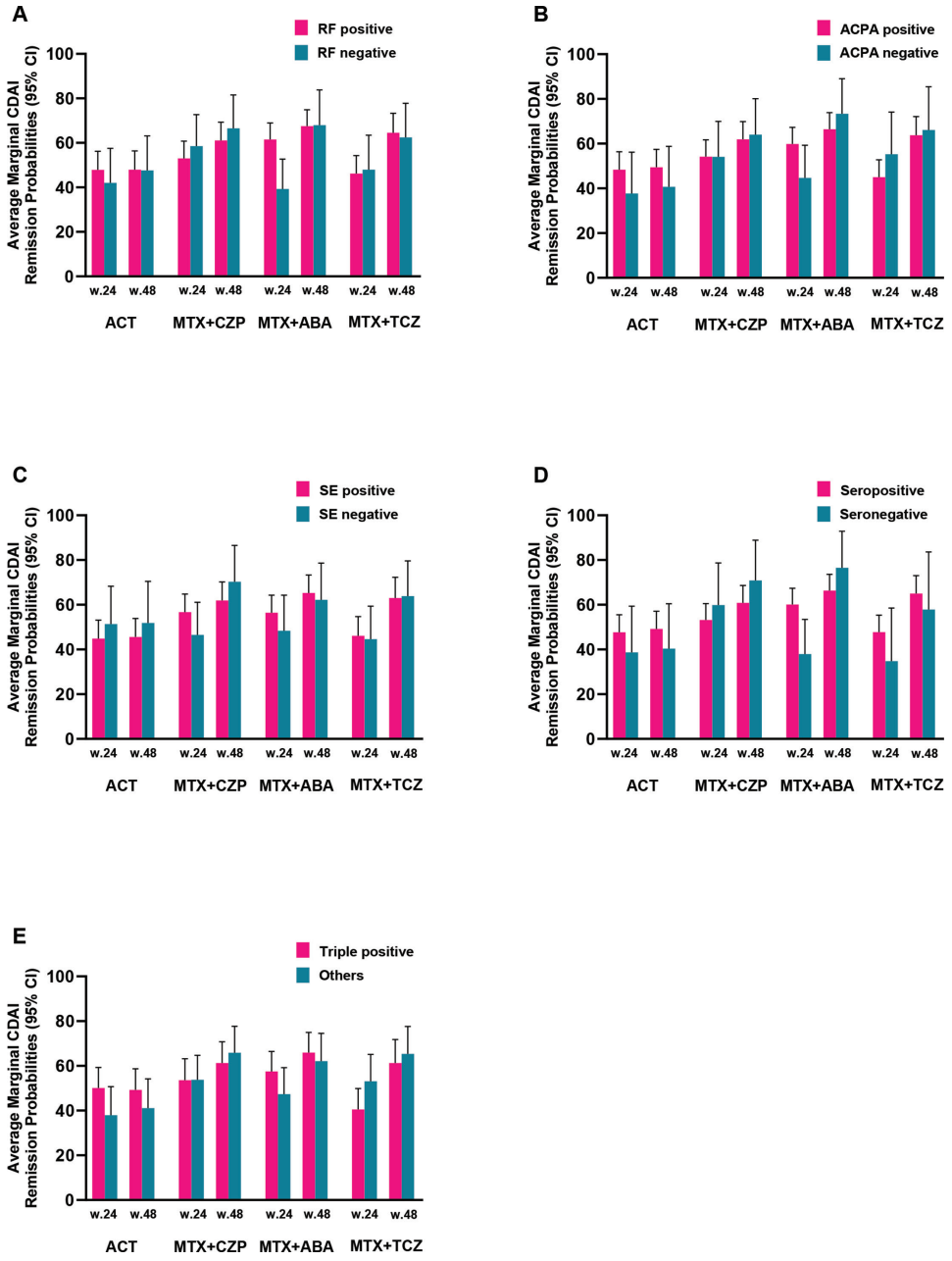

Figure 2 Probability of Clinical Disease Activity Index (CDAI) remission across subgroups based on RF, ACPA and shared epitope allele status. ACPA, anti-citrullinated protein antibodies; ABA, abatacept; ACT, active conventional treatment; CZP, certolizumab pegol; MTX, methotrexate; RF, rheumatoid factor; SE, shared epitope; TCZ, tocilizumab.

conventionally defined seronegative individuals.[29] The higher baseline disease activity observed among seronegative patients may also prolong the time to the treatment response, as observed in a previous study.[30]

Combining RF and ACPA positivity with SE allele did not improve the prediction of response. This can be clarified by noting that of 148 SE allele-negative patients, 58% were positive for ACPA and 63% were positive for RF in our study. Previous research has shown that independent from SE alleles, non-SE alleles, such as HLA-DRB1*09 and *15 may influence the production of ACPAs.[31 32]

Several studies have investigated the association between the presence of the SE allele and abatacept treatment at 24 weeks. While some studies have found an association between SE allele positivity and response to abatacept,[33 34] others have not.[11 35] One study showed that the SE HLA-DRB1*04:05 allele was independently associated with Simplified Disease Activity Index improvement with abatacept treatment regardless of anti-cyclic citrullinated peptide (anti-CCP) antibody titres at 3 months.[36]

Cha *et al* have investigated the effect of HLA-DRB1 genetic markers on treatment response to abatacept or TNF inhibitor in seropositive patients. They found no significant association between SE allele and treatment response but suggested that HLA-DRB1 position 11 (outside of the SE), as well as the valine-arginine-alanine (VRA) haplotype at amino acid positions 11, 71 and 74 of HLA-DRB1 were associated with treatment response to abatacept but not to TNF inhibitor.[11]

We also investigated the association between HLA-DRB1 valine at amino acid position 11, VRA haplotype and CDAI remission individually and in combination with RF and ACPA positivity. The only significant interaction was found with tocilizumab treatment, suggesting that VRA haplotype-positive

Table 2 Results of longitudinal data analyses estimating treatment effects on CDAI remission rates across subgroups based on RF, ACPA and shared epitope allele status

	Certolizumab pegol plus methotrexate versus active conventional treatment	P for interaction	Abatacept plus methotrexate versus active conventional treatment	P for interaction	Tocilizumab plus methotrexate versus active conventional treatment	P for interaction
	Averaged marginal differences (95% CI)					
Rheumatoid factor						
At week 24						
RF positive	5.1 (−6.3 to 16.5); p=0.38	0.35	13.6 (2.5 to 24.8); **p=0.017**	0.18	−1.7 (−13.4 to 9.9); p=0.77	0.55
RF negative	16.5 (−4.5 to 37.5); p=0.12	–	−2.7 (−23.2 to 17.8); p=0.80	–	6.0 (−16.0 to 27.9); p=0.59	–
At week 48						
RF positive	13.2 (1.5 to 24.9); **p=0.027**	0.65	19.6 (8.3 to 30.8); **p=0.001**	0.95	16.6 (4.5 to 28.8); **p=0.007**	0.88
RF negative	18.8 (−2.7 to 40.3); p=0.09	–	20.3 (−1.9 to 42.5); p=0.07	–	14.8 (−7.0 to 36.6); p=0.18	–
ACPA						
At week 24						
ACPA positive	5.8 (−5.2 to 16.8); p=0.30	0.44	11.5 (0.5 to 22.4); **p=0.04**	0.75	−3.4 (−14.6 to 7.8); p=0.55	0.16
ACPA negative	16.4 (−7.9 to 40.7); p=0.19	–	7.0 (−16.5 to 30.6); p=0.56	–	17.6 (−8.8 to 43.9); p=0.19	–
At week 48						
ACPA positive	12.5 (1.2 to 23.8); **p=0.03**	0.44	17.0 (6.0 to 28.0); **p=0.002**	0.26	14.4 (2.8 to 26.0); **p=0.015**	0.48
ACPA negative	23.3 (−0.8 to 47.4); p=0.058	–	32.7 (8.7 to 56.6); **p=0.007**	–	25.4 (−1.0 to 51.9); p=0.06	–
Shared epitope						
At week 24						
SE allele positive	11.9 (0.3 to 23.5); **p=0.045**	0.19	11.6 (0.2 to 23.0); **p=0.046**	0.27	1.2 (−10.7 to 13.2); p=0.84	0.54
SE allele negative	−4.8 (−27.1 to 17.5); p=0.67	–	−3.0 (−26.2 to 20.3); p=0.80	–	−6.8 (−29.4 to 15.8); p=0.56	–
At week 48						
SE allele positive	16.4 (4.7 to 28.1); **p=0.006**	0.86	19.7 (8.2 to 31.2); **p=0.001**	0.50	17.5 (5.0 to 29.9); **p=0.006**	0.70
SE allele negative	18.4 (−6.2 to 43.1); p=0.14	–	10.4 (−14.5 to 35.3); p=0.41	–	12.1 (−12.4 to 36.5); p=0.33	–
Serology status						
At week 24						
Seropositive RA	5.5 (−5.2 to 16.3); p=0.31	0.32	12.4 (1.7 to 23.1); **p=0.02**	0.38	0.1 (−10.8 to 11.1); p=0.98	0.81
Seronegative RA	21.1 (−6.9 to 49.2); p=0.14	–	−0.7 (−26.6 to 25.1); p=0.96	–	−4.0 (−35.4 to 27.5); p=0.81	–
At week 48						
Seropositive RA	11.7 (0.6 to 22.8); **p=0.038**	0.22	17.2 (6.4 to 28.0); **p=0.002**	0.21	15.9 (4.6 to 27.1); **p=0.006**	0.94
Seronegative RA	30.5 (3.5 to 57.5); **p=0.027**	–	36.2 (10.1 to 62.2); **p=0.007**	–	17.6 (−15.1 to 50.2); p=0.29	–
Triple status						
At week 24						
Triple positive	3.5 (−9.8 to 16.9); p=0.60	0.27	7.5 (−5.3 to 20.2); p=0.25	0.86	−9.6 (−22.8 to 3.6); p=0.15	**0.03**
Others	15.8 (−1.0 to 32.6); p=0.07	–	9.4 (−8.0 to 26.8); p=0.29	–	15.2 (−2.3 to 32.7); p=0.09	–
At week 48						
Triple positive	12.0 (−1.5 to 25.5); p=0.08	0.27	16.7 (3.7 to 29.7); **p=0.012**	0.75	12.0 (−2.1 to 26.2); p=0.10	0.31
Others	24.8 (7.2 to 42.4); **p=0.006**	–	20.9 (2.9 to 39.0); **p=0.023**	–	24.2 (6.3 to 42.2); **p=0.008**	–

Values are adjusted averaged marginal differences in rates with corresponding 95% CIs for three biological treatments, using active conventional treatment as the reference.
Bold indicates p < 0.05; Statistical significance p interaction < 0.1.
ACPA, anti-citrullinated protein antibodies; CDAI, Clinical Disease Activity Index; RA, rheumatoid arthritis; RF, rheumatoid factor; SE, shared epitope ; Seropositive, positive for ACPA, RF, or both; Triple positive, positive for RF, ACPA and shared epitope allele.

patients who were also positive for ACPA and RF had a less favourable effect than patients with other combinations when compared with active conventional treatment at 24 weeks. However, the interaction term was no longer significant at 48 weeks (online supplemental table S5, figure S3).

Even though the genetic link between the known HLA and non-HLA risk loci with RA has been established over the years, a considerable proportion of heritability remains unexplained. It appears from our study that the primary genetic risk factor for RA development, SE alleles, may have limited or no influence on treatment response, possibly due to differing mechanisms between RA pathogenesis and drug metabolism.

De Cock *et al* has previously analysed predictors of rapid radiological progression in patients with early RA and developed matrices using traditional parameters such as swollen joint count of 28 joints, RF, ACPA, CRP, erythrocyte sedimentation rate (ESR), erosions, gender and smoking.[37] However, the overall performance of these matrices was modest at best,[37] implying the need to explore variables beyond the classical ones.

Our study had some limitations. Owing to the relatively small numbers of RF-negative, ACPA-negative and SE allele-negative patients, the interactions had high p values even though the differences in estimated treatment responses were quite big. Furthermore, as a result of early terminations preceding 48 weeks or a few missed study appointments, clinical data was not available for every patient at each visit.

The strength of our study was that it consisted of patients with newly diagnosed RA who were randomly assigned to one of the four treatment groups. Centralised laboratory analyses were performed for the assessment of RF, ACPA and SE alleles. Furthermore, we analysed the subgroup effects of the baseline RF, ACPA and SE individually and in combinations longitudinally to provide robust effect and account for the differences in follow-up visits up to 48 weeks.

In conclusion, based on this large randomised controlled trial, we confirm that abatacept treatment was associated with a better response than active conventional treatment in the RF and/or ACPA positive subgroup at 24 weeks. However, because the interaction terms were not statistically significant, the effect observed in the positive subgroup was not significantly different from the effect in the negative subgroup. By 48 weeks, abatacept treatment showed a better response regardless of RF/ACPA status; the addition of SE allele status did not strengthen the association. Thus, no differences in treatment effect across RF, ACPA and SE allele subgroups were found in any of the biological treatment groups at 48 weeks. Moreover, ACPA, RF and SE allele genetic markers were not, alone or in combination, associated with clinical responses of importance sufficiently strongly to warrant implementation in clinical practice.

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