Can switching to abatacept therapy in patients with rheumatoid arthritis on background methotrexate reverse TNF-inhibitor-induced antinuclear autoantibody/ double-stranded DNA autoantibody conversion? An analysis of the AMPLE and ATTEST trials

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Abstract

Objective

To explore antinuclear autoantibody (ANA) and anti-double-stranded DNA (anti-dsDNA) autoantibody development during abatacept and tumour necrosis factor inhibitor (TNFi) treatment, and effects of switching from TNFi to abatacept in ANA/anti-dsDNA autoantibody-positive patients.

Methods

This was a post hoc analysis of biologic-naïve patients with active RA in ATTEST and AMPLE. In AMPLE, patients received subcutaneous abatacept or adalimumab (2 years). In ATTEST, patients received intravenous abatacept or infliximab (1 year), or placebo (6 months) then abatacept (6 months); at 1 year, all patients could receive abatacept (open-label long-term extension). Serum ANA/anti-dsDNA autoantibody levels were measured at baseline, Month 6 (ATTEST only), Years 1 and 2.

Results

At baseline, 25.7 and 0.9% (AMPLE), and 21.6 and 8.4% of patients (ATTEST) were ANA/anti-dsDNA autoantibody positive, respectively. More baseline ANA/anti-dsDNA autoantibody-negative patients became positive during TNFi than abatacept treatment. In ATTEST (TNFi group), 48.5% (48/99; ANA) and 48.3% (57/118; anti-dsDNA) of patients seroconverted to positive status by Year 1, falling to 22.4% (22/98 ANA) and 13.3% (15/113; anti-dsDNA) by Year 2 after switching to abatacept. Of ANA/anti-dsDNA autoantibody-positive patients at Year 1, 41.9% and 68.9%, were negative at Year 2.

Conclusion

ANA/anti-dsDNA seroconversion was more frequent with TNFi than abatacept therapy; TNFi-associated seroconversion decreased after switching from TNFi to abatacept.

Key words

autoantibodies, tumour necrosis factor-alpha/antagonists and inhibitors, biologic agents, disease-modifying anti-rheumatic drugs, rheumatoid arthritis

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ATTEST: ClinicalTrials.gov, NCT00095147.

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Introduction

Current recommendations for the management of rheumatoid arthritis (RA) emphasise the early use of methotrexate (MTX) and the addition of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in patients with an incomplete response to MTX, using a treat-to-target approach (1, 2). Patients receiving tumour necrosis factor inhibitor (TNFi) therapy can develop antinuclear autoantibodies (ANAs) and anti-double-stranded DNA (anti-dsDNA) autoantibodies; a small proportion of these patients develop clinical lupus (3-6). An association between this ANA seroconversion and the development of secondary non-response to bDMARD therapy has also been suggested (5). BDMARDs with different mechanisms of action are associated with varying immunogenic potential. In this context, the influence of sequential use of bDMARDs, which is common practice, on ANA/anti-dsDNA seroconversion is unclear.

Two trials have compared abatacept to a TNFi. ATTEST (NCT00095147) was a phase III trial comparing intravenous (IV) abatacept or IV infliximab with placebo (7); AMPLE (NCT00929864) was a phase IIIb trial comparing subcutaneous (SC) abatacept with SC adalimumab (8, 9).

The objectives of this analysis were to confirm a distinction in autoantibody induction between different biologic agents using data from the ATTEST and AMPLE studies, and to investigate the novel question of seroconversion to negative status following switch from a TNFi to abatacept using data from ATTEST.

Patients and methods

Trial design

The trial designs and primary results for both trials have been published (7-9). Patients had active RA, were biologic naïve, MTX inadequate responders and received background MTX. In ATTEST, patients were randomised (3:3:2) to IV abatacept (~10 mg/kg every 4 weeks), IV infliximab (3 mg/kg every 8 weeks), or placebo for 6 months (initial double-blind treatment) (7). At Month 6, placebo-treated patients switched to abatacept (blinding maintained); other patients continued blinded treatment. Patients completing the 1-year double-blind period were eligible to receive abatacept in an open-label long-term extension (10). In AMPLE, patients were randomised (1:1) to SC abatacept (125 mg every week) or SC adalimumab (40 mg every 2 weeks) for 2 years (8).

Serum ANA and anti-dsDNA autoantibody concentrations were measured at baseline, Month 6 (ATTEST only), Year 1, and Year 2. Samples were tested for ANA serostatus and positive samples were subsequently tested for anti-dsDNA autoantibodies (see Section 1 in the Supplementary Appendix for details).

Both studies were approved by institutional review boards and independent ethics committees at participating sites and were conducted in accordance with the Declaration of Helsinki (ClinicalTrials.gov registration numbers: AMPLE: NCT00929864; ATTEST: NCT00095147).

As this was a *post hoc* analysis, no specific consent was obtained above that received for each individual trial. All patients provided written informed consent prior to randomisation.

All the data generated or analysed during this study are included in this published article.

Endpoints and assessments

The primary endpoint for this *post hoc* analysis was the percentage of patients who reverted (baseline ANA/anti-dsDNA autoantibody positive to post-baseline negative) after switching from a TNFi to abatacept. An additional endpoint was the percentage of patients who seroconverted to ANA/anti-dsDNA autoantibody positive status with TNFi versus abatacept treatment.

Statistical analysis

Analyses were based on the intent-to-treat population. Due to the *post hoc* nature of these analyses, statistical significance could not be assigned. Descriptive summary statistics were provided for all continuous variables; absolute and relative frequency distributions were calculated for categorical data.

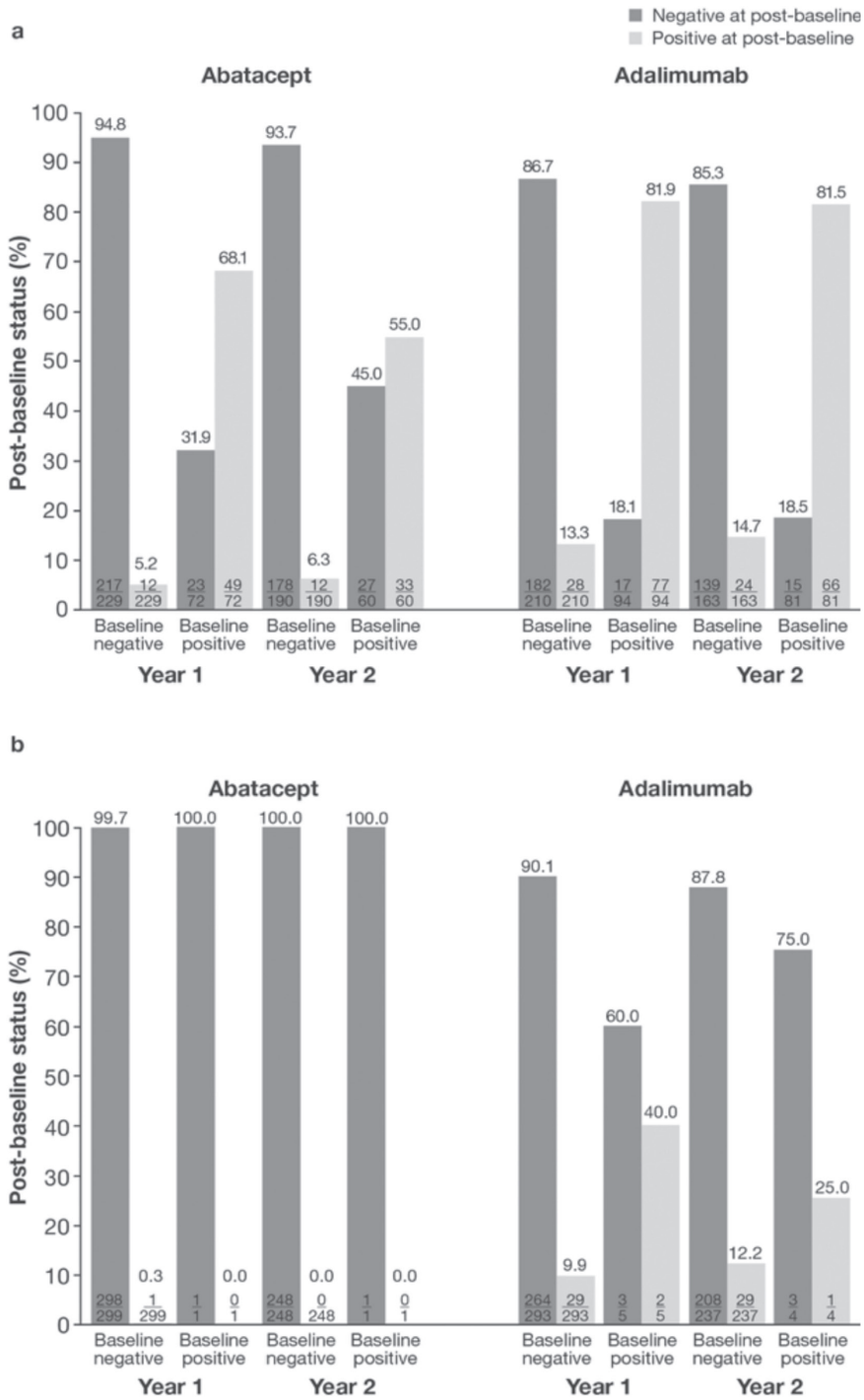

Fig. 1. AMPLE: Years 1 and 2 (**a**) ANA serostatus; (**b**) anti-dsDNA autoantibody serostatus.
The numbers at the base of each bar show *n*/*N*, and the number above each bar shows the percentage of patients with this post-baseline status.
ANA antinuclear autoantibody: anti-dsDNA anti-double-stranded DNA.

Results

Patient disposition and baseline characteristics

In ATTEST, 156 patients received abatacept, 165 infliximab, and 110 placebo in the double-blind period; 107 placebo patients switched to abatacept at Month 6. In the open-label abatacept period, 132, 136, and 104 patients originally randomised to abatacept, infliximab, and placebo, respectively, received abatacept. In AMPLE, 318 patients received abatacept and 328 adalimumab. In both studies, baseline characteristics were similar across treatment arms (see Table SI in the Supplementary Appendix) (7, 9).

ANA/anti-dsDNA autoantibody positivity at baseline

At baseline in ATTEST, 93/431 (21.6%) patients (32 IV abatacept, 37 IV infliximab, and 24 placebo) were ANA positive and 36 (8.4%) patients (11 IV abatacept, 15 IV infliximab, and 10 placebo) were anti-dsDNA autoantibody positive. At baseline in AMPLE, 166/646 (25.7%) patients (72 SC abatacept and 94 SC adalimumab) were ANA positive and 6 (0.9%) patients were anti-dsDNA autoantibody positive (1 SC abatacept and 5 SC adalimumab).

Conversion to ANA/anti-dsDNA autoantibody positive status with TNFis vs. abatacept (baseline negative to post-baseline positive)

In both ATTEST (see: Fig. S1 in the Supplementary Appendix) and AMPLE (Fig. 1), a higher percentage of TNFi-treated than abatacept-treated patients had converted to ANA/anti-dsDNA autoantibody positive status (baseline negative to post-baseline positive) at Year 1; this trend persisted during Year 2 of AMPLE (Fig. 1). In ATTEST, for which placebo data were available at Month 6, ANA seroconversion (baseline negative to post-baseline positive) at Month 6 occurred in 2/115 (1.7%) patients treated with abatacept, 38/118 (32.2%) patients treated with infliximab, and 4/81 (4.9%) patients treated with placebo; anti-dsDNA seroconversion had occurred in 1/128 (0.8%) patient treated with abatacept, 51/132 (38.6%) patients treated with infliximab, and 4/93 (4.3%) treated with placebo.

Reversion to ANA/anti-dsDNA autoantibody negative status following switch from a TNFi to abatacept (ATTEST study only)

Among infliximab-treated patients who entered the open-label abatacept treatment period, conversion from baseline ANA/anti-dsDNA autoantibody negative to positive at Year 1 occurred in 48/99 (48.5%; ANA) and 57/118 (48.3%; anti-dsDNA) patients. In this cohort, the numbers of ANA/anti-ds-

Table I. Number of patients with ANA autoantibody seroconversion (Year 1 to Year 2 in ATTEST), by baseline status.*

ANA seroconversion from Year 1 to Year 2 by baseline ANA status							
		Abatacept/placebo-to-abatacept Year 2 status			Infliximab-to-abatacept Year 2 status		
Baseline status	Year 1 status	Negative	Positive	Total	Negative	Positive	Total
ANA negative	ANA negative	140	14	154	48	3	51
	ANA positive	8	3	11	26	19	45
	Total	148	17	165	74	22	96
ANA positive	ANA negative	14	4	18	2	2	4
	ANA positive	4	26	30	5	24	29
	Total	18	30	48	7	26	33
Overall	ANA negative	154	18	172	50	5	55
	ANA positive	12	29	41	31	43	74
	Total	166	47	213	81	48	129

*Analysis in patients with available baseline, Year 1 and Year 2 ANA data.
ANA: antinuclear autoantibody.

Table II. Number of patients with anti-dsDNA autoantibody seroconversion (Year 1 to Year 2 in ATTEST), by baseline status.*

Anti-dsDNA antibody seroconversion from Year 1 to Year 2 by baseline anti-dsDNA status							
		Abatacept/placebo-to-abatacept Year 2 status			Infliximab-to-abatacept Year 2 status		
Baseline status	Year 1 status	Negative	Positive	Total	Negative	Positive	Total
Anti-dsDNA negative	Anti-dsDNA negative	187	2	189	55	2	57
	Anti-dsDNA positive	4	2	6	42	12	54
	Total	191	4	195	97	14	111
Anti-dsDNA positive	Anti-dsDNA negative	1	1	2	1	0	1
	Anti-dsDNA positive	2	12	14	4	9	13
	Total	3	13	16	5	9	14
Overall positive	Anti-dsDNA negative	188	3	191	56	2	58
	Anti-dsDNA positive	6	14	20	46	21	67
	Total	194	17	211	102	23	125

*Analysis in patients with available baseline, Year 1 and Year 2 anti-dsDNA data.
anti-dsDNA: anti-double-stranded DNA.

DNA autoantibody-positive patients fell to 22/98 (22.4%; ANA) and 15/113 (13.3%; anti-dsDNA) at Year 2, following the transition to abatacept.

In patients who switched from infliximab to abatacept and were ANA positive at Year 1 (analysis in 74 patients with available baseline, Year 1, and Year 2 data; Table I), 31/74 (41.9%) had reverted to ANA negative status and 43/74 (58.1%) remained ANA positive at Year 2. Among the 31 patients with ANA reversion (positive at Year 1 to negative at Year 2) on switching from infliximab to abatacept, 26 had previously converted to ANA/anti-dsDNA autoantibody-positive status (baseline negative to positive at Year 1) during infliximab treatment and 5 were previously ANA/anti-dsDNA autoantibody positive at baseline (Table I). Among the 43 patients who remained ANA positive from Year 1 to Year 2, 19 had previously seroconverted (baseline negative to positive at Year 1) while taking infliximab and 24 had been ANA positive at baseline (Table I).

In patients who switched from infliximab to abatacept and were anti-dsDNA positive at Year 1 (analysis in 67 patients with available baseline, Year 1, and Year 2 data; Table II), 46/67 (68.7%) reverted to anti-dsDNA autoantibody negative and 21/67 (31.3%) remained anti-dsDNA autoantibody positive at Year 2. Among the 46 patients with anti-dsDNA autoantibody reversion (positive at Year 1 to negative at Year 2) on switching from infliximab to abatacept, 42 had previously seroconverted (baseline negative to positive at Year 1) on infliximab and 4 had been previously anti-dsDNA autoantibody positive at baseline (Table II). Among the 21 patients who remained anti-dsDNA autoantibody positive from Year 1 to Year 2, 12 had seroconverted (baseline negative to positive at Year 1) during infliximab treatment and 9 were anti-dsDNA autoantibody positive at baseline (Table II).

Discussion

Autoantibodies to cellular and nuclear antigens, such as ANA and anti-dsDNA antibodies, result from the dysregulation of the immune system and can be associated with autoimmune diseases. This is the first analysis to assess how the successive use of bDMARDs (infliximab to abatacept) affects ANA and anti-dsDNA autoantibody seroconversion and seroreversion in patients with RA. Our results suggest that switching ANA/anti-dsDNA autoantibody-positive patients from a TNFi to abatacept may be associated with reversion to an ANA/anti-dsDNA autoantibody-negative status in some patients.

In patients with RA, TNFi-induced ANA and/or anti-dsDNA autoantibody seroconversion is well-described. Whilst in the main, this does not hold clinical relevance, ANA positivity during TNFi treatment has been associated with the development of emergent autoimmune diseases, including lupus and vasculitis, in a minority of patients (4, 6, 11). Only two TNFis (infliximab and adalimumab) were studied here, and it is possible that rates of ANA and dsDNA positivity could differ among other TNFis. Whether ANA and anti-dsDNA autoantibody production influences treatment efficacy requires further investigation. One study has reported that RA patients with ANA treated with infliximab have significantly higher disease activity scores than those without (4). An association between seroconversion and secondary non-responsiveness

has also been suggested (6). In contrast, one study found therapeutic responses to be independent of ANA and anti-dsDNA autoantibody titres (11).

In our report, seroconversion to ANA or anti-dsDNA autoantibody positivity was lower in abatacept- than in TNFi-treated patients. Furthermore, in ATTEST, the proportion of patients who were ANA/anti-dsDNA autoantibody positive decreased after switching from infliximab to abatacept. This finding may reflect the different mechanisms of action of abatacept and TNFi. Notably, abatacept acts upstream in the inflammatory process, inhibiting CD28-CD80/86 costimulation that is required for full T-cell activation and, thus, the T-cell help required for antibody production. Although not specifically studied, no relationship of adverse events with the development of ANA or anti-dsDNA autoantibodies was noted in either trial.

The association between TNFi treatment and autoantibody development reported here is consistent with findings from other studies. It has been reported that approximately half of infliximab-treated patients in clinical trials who were ANA negative at baseline develop ANAs compared with approximately one fifth of placebo-treated patients; whereas anti-dsDNA autoantibodies develop in approximately one fifth of infliximab-treated and no placebo-treated patients (3, 12).

The association with autoantibody development may not be consistent across all agents that target TNF, with seroconversion rates in patients with RA generally being highest with the chimeric, and thus more immunogenic, molecule infliximab (4, 6, 11). In the AMPLE study, which provides direct comparative data, ANA seroconversion rates were lower with abatacept than with TNFi, and confirm the results from a previous study (6). Our data now suggest that switching to abatacept could reverse this TNFi-induced ANA seropositivity in some patients. As noted above, these findings could reflect inhibition of B-cell function (13) and autoantibody production due to T-cell costimulation blockade (14), although the seroreversion could also occur simply as a result of removal of the TNFi.

In the ATTEST study, it is interesting to note that most of the infliximab-treated patients who became negative for ANA or anti-dsDNA autoantibodies after treatment with abatacept were not positive at baseline, but rather had converted to a positive status while on infliximab. Further study is required, but this finding may suggest that autoantibodies that develop while on TNFi therapy are more transient than those that were present prior to TNFi therapy.

Limitations of this analysis should be considered. This analysis did not investigate whether an association existed between autoantibody positivity and clinical efficacy and safety outcomes. A further limitation of this analysis is that it was a *post hoc* analysis and therefore significance cannot be assigned. In addition, each of the active agents in ATTEST was compared with placebo; therefore, comparisons of abatacept and infliximab should be interpreted with caution (7). The decrease in ANA/anti-dsDNA autoantibodies after switching to abatacept could be the result of discontinuing TNFi therapy, or starting abatacept therapy, or a combination of both. The ability of abatacept to actively decrease ANA and dsDNA antibodies in patients with RA, as opposed to their gradual reduction after discontinuing a TNFi, was not possible to confirm in this study due to the lack of a control group in ATTEST (patients who discontinued TNFi but did not start abatacept). A study randomising patients on TNFi who had developed ANA/anti-dsDNA autoantibodies to continued TNFi, placebo, or abatacept therapy could help to better understand the correlative changes observed in this study.

Finally, the effect of ANA/anti-dsDNA autoantibody seroconversion on efficacy and safety outcomes was not studied in this analysis; therefore, the clinical relevance of these findings is unknown.

Conclusions

In patients with RA, TNFi therapy with infliximab or adalimumab was associated with greater ANA and anti-dsDNA autoantibody induction than abatacept therapy. Furthermore, in some patients, ANA and anti-dsDNA autoantibodies that had developed during TNFi treatment decreased upon switching from infliximab to abatacept. This analysis provides insights which may assist with clinical decisions. Abatacept may provide a good treatment option for patients for whom there are concerns regarding positive ANA and/or dsDNA antibodies. Moreover, even in the absence of a control group, these data can provide confidence in switching patients from a TNFi to abatacept.

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Supplementary Appendix

Section 1: ANA/anti-dsDNA autoantibody testing

Samples were tested for ANAs by indirect fluorescence assays using HEp-2 cell-line substrate, and for anti-dsDNA autoantibodies by the Farr method (ATTEST) or indirect fluorescence assays using Crithidia luciliae substrate (AMPLE). ANA serostatus was categorised as negative or positive, corresponding to the following dilutions, respectively: <1:160 and ≥1:160. Anti-dsDNA serostatus was categorised as either negative or positive, corresponding to <5.4 IU/mL and ≥5.4 IU/mL (Farr method; ATTEST), and <1:10 and ≥1:10 (indirect fluorescence assay; AMPLE), respectively.

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Table SI. Baseline characteristics in the AMPLE and ATTEST trials.

	AMPLE (1)		ATTEST (2)		
	Abatacept + MTX (n=318)	Adalimumab + MTX (n=328)	Abatacept + MTX (n=156)	Placebo + MTX (n=110)	Infliximab + MTX (n=165)
Age, years	51.4 (12.6)	51.0 (12.8)	49.0 (12.5)	49.4 (11.5)	49.1 (12.0)
Female, %	81.4	82.3	83.3	87.3	82.4
Disease duration, years	1.9 (1.4)	1.7 (1.4)	7.9 (8.5)	8.4 (8.6)	7.3 (6.2)
Tender joints, n	25.4 (15.3)	26.3 (15.8)	31.6 (13.9)	30.3 (11.7)	31.7 (14.5)
Swollen joints, n	15.8 (9.8)	15.9 (10.0)	21.3 (8.6)	20.1 (7.0)	20.3 (8.0)
DAS28 score	5.5 (1.1)*	5.5 (1.1)*	6.9 (1.0)†	6.8 (1.0)†	6.8 (0.9)†
HAQ-DI (0–3) score	1.5 (0.7)	1.5 (0.7)	1.8 (0.6)	1.8 (0.7)	1.7 (0.7)
MTX dose, mg/week	17.5 (6.4)	17.3 (6.2)	16.5 (3.7)	16.6 (3.7)	16.3 (3.6)

Data are mean (SD) unless otherwise stated. *Based on C-reactive protein level. †Based on erythrocyte sedimentation rate level. DAS28: Disease Activity Score in 28 joints; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; SD: standard deviation.

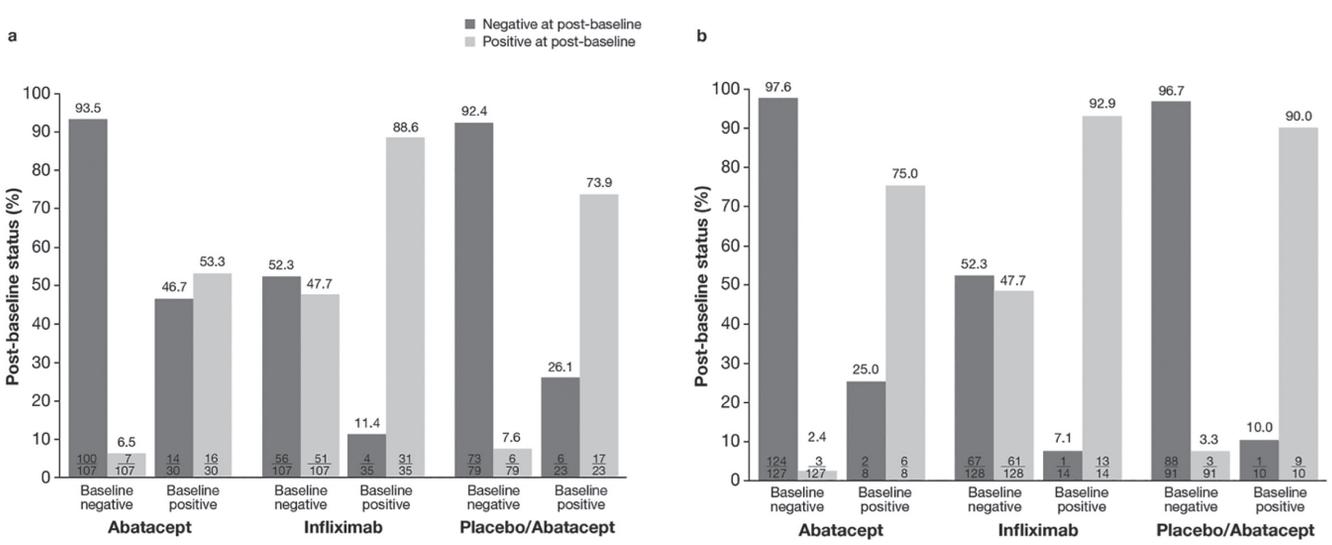

Fig. S1. (**a**) ANA serostatus at Year 1 in ATTEST; (**b**) anti-dsDNA autoantibody serostatus at Year 1 in ATTEST. At Month 6, patients randomised to placebo started abatacept. The numbers at the base of each bar show *n*/*N*, and the number above each bar shows the percentage of patients with this post-baseline status. ANA: antinuclear autoantibody; anti-dsDNA: anti-double-stranded DNA.