Efficacy and safety of infliximab or adalimumab, versus abatacept, in patients with rheumatoid arthritis: ATTEST–AMPLE network randomized trial

Our objective was to assess the efficacy of infliximab, adalimumab and abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate. The purpose of this type of analysis is to combine evidence from direct and indirect sources into one overall objective. The meta-data set included results from the ATTEST and AMPLE studies. Major outcomes concerned the benefits and harm after 1 year on therapy; coprimary outcomes patients achieving a 50% response on the ACR improvement criteria, extracted from the papers, and the number of withdrawals related to adverse events, respectively. Statistical analyses were based on mixed-effects logistic regression, using an arm-based, random-effects model respecting randomization within each study. Following indirect comparisons across all three groups, we conclude that infliximab, at the recommended dose, is less efficacious than abatacept and potentially also adalimumab, and that adalimumab and abatacept are approximately equivalent both in terms of benefit and short-term harm assessment (up to 1 year).

KEYWORDS: abatacept ▪ adalimumab ▪ infliximab ▪ meta-analysis ▪ methotrexate ▪ rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness and destruction of synovial joints, leading to severe disability and premature mortality [1,2]. The disease causes disability (with loss of working capacity and early retirement) and risk of premature death if insufficiently treated [3,4]. The enormous consequences for the individual and for healthcare and socioeconomic systems can only be prevented by effective treatments. Inflammation in patients presenting with RA should be suppressed as early as possible [5,6].

The management of RA rests on several principles [7,8]. Pharmacological intervention comprises disease-modifying antirheumatic drugs (DMARDs), but also NSAIDs and glucocorticoids (GCs). During the last 10–20 years, highly effective DMARDs have continued to emerge [9,10] – in particular, biological agents that target TNF-α, the IL-1 receptor, the IL-6 receptor, B lymphocytes and T-cell costimulation [11]. The term 'biological' describes treatments developed and produced in live cell systems; biological agents are also referred to as biological therapies or cytokine modulators [12].

TNF-α blockers differ in composition, precise mechanism of action, pharmacokinetics and biopharmaceutical properties [9,13]. The TNF-α blocker category currently includes the following drugs: adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. Infliximab is a chimeric (human and mouse) monoclonal antibody against TNF-α [14]. Adalimumab and golimumab are 100% human TNF-α monoclonal antibodies, certolizumab is a Fc fragment combined with PEG, and etanercept is a receptor [13]. For all TNF-α blocking agents, a sustained clinical benefit in RA patients with an inadequate response to methotrexate (MTX) occurs when administered concomitantly with MTX [9,15,16]. Other licensed biological agents with alternative mechanisms of action include tocilizumab (targeting IL-6), rituximab (targeting B lymphocytes), and abatacept (T-cell modulator) [13].

An important role for activated T cells in RA immunopathology makes T-cell activation a rational therapeutic target for intervention. Abatacept is the first in a new class of agents for treating RA that selectively modulate the costimulatory signal required for full T-cell activation. The efficacy of abatacept has previously been demonstrated to be comparable to other biologics in patients with RA, who demonstrate an inadequate response to MTX [15,17]. Abatacept is approved for the treatment of RA patients with inadequate response to one or more DMARDs, including MTX or a TNF-α blocker; abatacept can be administered either intravenously (iv.) or subcutaneously (sc.) [18].

For RA, treatments aim to relieve joint pain, swelling and stiffness, improve function and reduce or inhibit joint damage. In the past decade, biological agents – especially TNF inhibitors – have resulted in hitherto unseen

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therapeutic benefit, although the frequency and degree of responses are still restricted [19]. The comparative effectiveness associated with use of these drugs has indicated that if drugs are used at the right dose [9,10], their efficacy is equal, with a number-needed to treat of approximately four patients to achieve a 50% response on the ACR improvement criteria (ACR50). This statistic means that differences among individual biologics are very hard to test (i.e., difficult to succeed in superiority trials), which is probably the reason why very few head-to-head comparison trials are available to date [20–24].

One way to circumvent the difficulties of comparing one biologic with another in RA is the indirect network meta-analysis approach [25–27], which may give indications of individual assets or drawbacks of the products. We used this approach, combining data from the ATTEST and AMPLE studies – comparing infliximab and adalimumab with abatacept in patients with RA to assess the comparative efficacy of infliximab, adalimumab and abatacept in patients with RA, and an inadequate response to MTX.

Methods

Trial design & participants

We combined data from only the ATTEST and AMPLE studies as, apart from these two randomized trials, no other trials have compared biological agents in patients with concomitant use of MTX. Thus, we did not do a formal systematic review and meta-analysis. The ATTEST-AMPLE network randomized trial was based on a merged data set: the meta-data set combines direct and indirect trial results from the ATTEST [20] and AMPLE [22] studies.

The ATTEST study was designed to obtain data on the efficacy and safety of iv. administered abatacept by weight or infliximab 3 mg/kg versus placebo in RA. The study utilized a double-blind (i.e., double-dummy technique), randomized (3:3:2), placebo-controlled design for the first 6 months to validate efficacy responses, and the study duration allowed some comparison of the safety profile of the active biologic treatment groups over 1 year. It is notable that the analyses did not compare active treatments but, rather, compared each biologic to a placebo. Our work focused on data available after 1 year, enabling a direct comparison between abatacept and infliximab in a randomized trial (NCT00095147) [101].

The AMPLE study randomly assigned RA patients in a 1:1 ratio to receive sc. abatacept 125 mg, administered once per week (without an iv. loading dose), or adalimumab 40 mg administered sc. every other week, both given in combination with MTX. The trial was single blind, utilizing a blinded evaluator. Patients were stratified by disease activity, according to those with high disease activity (defined as a disease activity score in 28 joints [DAS28]-C-reactive protein score [CRP] of >5.1) and those with moderate disease activity (defined as a DAS28-CRP of ≥3.2 and ≤5.1). The primary end point in the AMPLE study was treatment noninferiority between sc. abatacept and sc. adalimumab (NCT00929864) [102].

Both trial sets included patients who met the ACR criteria for RA [1], were at least 18 years of age, and had an inadequate response to MTX.

Interventions

ATTEST study

Abatacept was dosed according to weight. Patients weighing less than 60 kg, 60–100 kg or more than 100 kg, received 500, 750 or 1000 mg of abatacept, respectively. Infliximab was dosed at 3 mg/kg for all patients. Abatacept was administered by iv. infusion on days 1, 15 and 29, and every 28 days thereafter, up to and including day 337 (with normal saline received on day 43). Infliximab was administered on days 1, 15, 43 and 85, and every 56 days thereafter (normal saline was received at the remaining visit days). Two iv. bags were infused simultaneously to ensure blinding to treatment group assignment, one over 30 min (abatacept or placebo) and one over 2 h (infliximab or placebo).

AMPLE study

Patients were assigned to receive 125 mg abatacept, administered sc. once per week (without an iv. loading dose), or 40 mg adalimumab, administered sc. every other week, both were given in combination with MTX.

Outcome measures

The primary outcome measure evaluated in the ATTEST study was a reduction in disease activity, measured by DAS28 with abatacept versus placebo at 6 months [20]. The primary outcome measure in the AMPLE study – for determining the noninferiority of sc. abatacept compared with sc. adalimumab – was the proportion of patients in each group achieving a 20% response on the ACR improvement criteria (ACR20) at 1 year [22]. For the purpose of the ATTEST–AMPLE network trial, we included all the outcomes that were available in both trial publications [20,22]. However, we decided *a priori* to consider the following major outcomes as primary measures

for benefit and harm after 1 year of therapy [10]: benefit was defined as ACR50 [28]; and harm was determined by the number of withdrawals related to adverse events [29].

Secondary efficacy outcomes consisted of ACR20 and a 70% level of improvement according to the ACR response criteria (ACR70), achievement of clinical remission (defined as a DAS28-CRP score of ≤2.6) and low disease activity (i.e., DAS28-CRP score of ≤3.2). Safety outcomes – classified using the Medical Dictionary for Regulatory Activities – were also extracted for all the domains reported in both trial publications [20,22]; including deaths, serious adverse events (SAEs), drug-related SAEs, discontinuation due to SAEs, adverse events (AEs), drug-related AEs, discontinuation due to AEs, serious infections and autoimmune events.

Sample size

The ATTEST study based its sample size and power calculation on the ability to detect a treatment difference in the primary analysis of a mean change from baseline in DAS28 for the abatacept versus placebo groups at day 197. The AMPLE study based its sample size estimation on the assumption of a 2.5% one-sided level of significance with 93% power to detect a difference between groups, and a 12% noninferiority margin (one that preserves at least 50% of the treatment effect). This margin allows for a maximum difference of -4.7% in the ACR20 response between sc. abatacept and sc. adalimumab, a difference that was considered to be clinically meaningful. As a consequence of the original trial publications [20,22], the ATTEST–AMPLE network trial included 474 and 165 out of 328 patients on abatacept and infliximab/adalimumab, respectively. A two-independent-binomial-proportions χ^2 statistic approximation with a sample size of 450 per group has an approximate power of 86% when the proportions responding are 0.5 and 0.4 (i.e., corresponding to a number needed to treat of ten patients). Thus, we considered this particular evidence synthesis (ATTEST–AMPLE network) project to have a reasonable power to detect a difference between abatacept and infliximab/adalimumab.

Randomization & blinding

Both studies were multicenter, multinational, randomized, double-/single-blind, controlled trials. The sequence generation and allocation concealment were based on a central randomization system, apparently generated within Bristol-Myers Squibb.

The masking was apparently sufficient in the ATTEST study, which reported using two (identically appearing) iv. bags to infuse simultaneously to ensure blinding to treatment group assignment, one over 30 min (abatacept or placebo) and one over 2 h (infliximab or placebo) [20]. By contrast, in the AMPLE study, double-blinding for the study drugs was not feasible due to logistic barriers that did not permit masking of the adalimumab syringes: patients were not blinded with regard to their study drug; whereas clinical assessors were blinded with regard to each patient's treatment [22]. According to the study publication, the blinded assessors evaluated the patients' joints, assessed disease activity, and defined AE causality. In addition, Weinblatt *et al.* report that different physicians reviewed and approved all of the data entry form, but did not contribute to the data collection [22].

Statistical analysis

The statistical methods used to compare groups for primary and secondary outcomes in the original trial reports are available elsewhere [20,22]. All data analyses in the present study were carried out according to a pre-established analysis plan and were achieved applying SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA).

All analyses were performed using the modified intention-to-treat population, which included all patients who were randomized and who had received at least one dose of study drug. Patients who discontinued the study prematurely were considered nonresponders, subsequent to the time of discontinuation, for ACR20, ACR50 and ACR70 responses, DAS responses and clinically meaningful Health Assessment Questionnaires for RA. For the purpose of comparing all interventions in the network (including both direct and indirect evidence), we applied a mixed-effects logistic regression using an arm-based, random-effects model within an empirical Bayes framework [27]; the generalized linear mixed model incorporates a vector of random effects and a design matrix for the random effects [30] (i.e., recognizing that the ATTEST and AMPLE studies are mutually independent). On the basis of the comparison of the individual odds and odds ratios (ORs) from indirect and direct evidence, respectively, we estimated the pairwise comparisons for benefit and harm as the combined OR with 95% CIs. We considered two-sided p-values less than 0.05 and 95% CIs that did not include 1 to be statistically significant.

Results

Patient demographics and clinical characteristics

In this pooled analysis, we included 967 patients with RA in the modified intention-to-treat population. The ATTEST study randomly assigned patients with disease duration of ≥5 years to treatment with abatacept (n = 156) or infliximab (n = 165) plus MTX; the AMPLE study randomly assigned patients with disease duration ≥1 year to abatacept (n = 318) or adalimumab (n = 328) plus MTX (Table 1). As expected from the inclusion criteria, there were differences in disease duration, but other baseline demographic and clinical characteristics did not differ between treatment groups within studies [20,22]. There was a numerical tendency towards higher disease activity in the ATTEST study (Table 1).

Reported efficacy and safety

Table 2 presents the outcome of each study, assessed at 1-year follow-up. The results from the ATTEST study indicate that iv. abatacept could be more efficacious than iv. infliximab, although the study was not designed or powered to show superiority. The authors concluded that, overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer SAEs, serious infections, acute infusional events and discontinuations due to AEs than the infliximab group [20]. The results from the AMPLE study, on the other hand, demonstrate that sc. abatacept and sc. adalimumab have comparable efficacy in patients with RA and over 1 year of treatment (Table 2). Table 2 presents the original results from the ATTEST and AMPLE study.

Network trial analyses

Table 3 presents a summary of the findings of the ATTEST–AMPLE network randomized trial of infliximab or adalimumab versus abatacept for RA. Compared with infliximab (iv.), abatacept (iv./sc.) was associated with a significantly higher likelihood of achieving an ACR50 response (OR: 1.49; 95% CI: 1.03–2.15; p = 0.032) and less likely to result in discontinuation due to adverse events (OR: 0.45; 95% CI: 0.21–0.96; p = 0.040). By contrast, with adalimumab (sc.) the ACR50 response rate was comparable to the response rates observed with abatacept (iv./sc.) as also shown in Table 3 (OR: 1.00; 95% CI: 0.75–1.32; p = 0.99). Abatacept (iv./sc.) trended toward fewer withdrawals from AEs compared with adalimumab (sc.; OR: 0.54; 95% CI: 0.27–1.05; p = 0.07). The trial network also generated an indirect estimate comparing

Table 1. Baseline demographic and clinical characteristics of patients in the intent-to-treat populations: ATTEST and AMPLE studies.

Variable	Study, drugs, administration method (n)			
	ATTEST, abatacept + MTX, iv. (156)	***ATTEST, infliximab + MTX, iv. (165)***	***AMPLE, abatacept + MTX, sc. (318)***	***AMPLE, adalimumab + MTX, sc. (328)***
Age, years (SD)	49.0 (12.5)	49.1 (12.0)	51.4 (12.6)	51.0 (12.8)
Females, n (%)	130 (83.3)	136 (82.4)	259 (81.4)	270 (82.3)
Geographic region: – North America, n (%) – South America, n (%) – Other, n (%)	 16 (10.3) 93 (59.6) 47 (30.1)	 5 (9.1) 96 (58.2) 54 (32.7)	 230 (72.3) 88 (27.7) 0 (0.0)	 235 (71.6) 93 (28.4) 0 (0.0)
Disease duration, years (SD)	7.9 (8.5)	7.3 (6.2)	1.9 (1.4)	1.7 (1.4)
Tender joints, n (SD)	31.6 (13.9)	31.7 (14.5)	25.4 (15.3)	26.3 (15.8)
Swollen joints, n (SD)	21.3 (8.6)	20.3 (8.0)	15.8 (9.8)	15.9 (10.0)
CRP, mg/dl (SD)	3.1 (2.7)	3.3 (3.2)	1.6 (2.1)	1.5 (2.8)
DAS28-ESR†/-CRP‡ (SD)	6.9 (1.0)	6.8 (0.9)	5.5 (1.1)	5.5 (1.1)
HAQ-DI, 0–3 (SD)	1.8 (0.6)	1.7 (0.7)	1.5 (0.7)	1.5 (0.7)
Rheumatoid factor positive, n (%)	136 (87.2)	140 (84.8)	240.0 (75.5)	254.0 (77.4)
Concomitant corticosteroids, n (%)	118 (75.6)	118 (71.5)	162.0 (50.9)	165.0 (50.3)

†ATTEST only.
‡AMPLE only.
CRP: C-reactive protein; DAS28: Disease activity score in 28 joints; ESR: Erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire Disability Index; iv.: Intravenous; MTX: Methotrexate; sc.: Subcutaneous; SD: Standard deviation.

Table 2. Efficacy and safety summaries in the ATTEST and AMPLE studies.

Outcome	Study, drugs (administration method)			
	ATTEST, abatacept + MTX (iv.)	***ATTEST, infliximab + MTX (iv.)***	***AMPLE, abatacept + MTX (sc.)***	***AMPLE, adalimumab + MTX (sc.)***
Clinical efficacy				
ACR20, n (%)	113 (72.4)	92 (55.8)	206 (64.8)	208 (63.4)
ACR50, n (%)	71 (45.5)	60 (36.4)	147 (46.2)	151 (46.0)
ACR70, n (%)	41 (26.3)	34 (20.6)	93 (29.2)	86 (26.2)
LDAS (DAS28)†, n (%)	55 (35.3)	37 (22.4)	189 (59.4)	201 (61.3)
Remission (DAS28)‡, n (%)	29 (18.6)	20 (12.1)	138 (43.4)	137 (41.8)
Adverse events				
Deaths, n (%)	1 (0.6)	2 (1.2)	1 (0.3)	0 (0.0)
SAEs, n (%)	15 (9.6)	30 (18.2)	32 (10.1)	30 (9.1)
Related SAEs, n (%)	5 (3.2)	14 (8.5)	8 (2.5)	11 (3.4)
Discontinued due to SAEs, n (%)	4 (2.6)	6 (3.6)	4 (1.3)	10 (3.0)
AEs, n (%)	139 (89.1)	154 (93.3)	280 (88.1)	283 (86.3)
Related AEs, n (%)	72 (46.2)	96 (58.2)	111 (34.9)	131 (39.9)
Discontinued due to AEs, n (%)	5 (3.2)	12 (7.3)	11 (3.5)	20 (6.1)
Serious infections, n (%)	3 (1.9)	14 (8.5)	7 (2.2)	9 (2.7)
Autoimmune events, n (%)	2 (1.3)	1 (0.6)	10 (3.1)	4 (1.2)

†DAS28-CRP score of ≤3.2.
‡DAS28-CRP score of ≤2.6.
ACR20: 20% response on the ACR improvement criteria; ACR50: 50% response on the ACR improvement criteria; ACR70: 70% response on the ACR improvement criteria; AE: Adverse event; DAS28: Disease activity score in 28 joints; iv.: Intravenous; LDAS: Low disease activity score; MTX: Methotrexate; SAE: Serious adverse event; sc.: Subcutaneous.

iv. infliximab with sc. adalimumab: compared with infliximab, the use of adalimumab was associated with a statistically significant higher likelihood of achieving an ACR50 response (OR: 1.49; 95% CI: 1.02–2.19; p = 0.041) and equally likely to result in discontinuation due to an adverse event (OR: 0.83; 95% CI: 0.39–1.74; p = 0.62).

The same pattern applied for the majority of secondary outcomes. Across all the efficacy outcomes, infliximab (iv.) was consistently inferior to abatacept (iv./sc.). Except for ACR70 (p = 0.055) and DAS28-remission (p = 0.084), abatacept was statistically significantly superior to infliximab (p ≤ 0.032). Across secondary safety outcomes, infliximab apparently caused more SAEs (p = 0.0056), drug-related SAEs (p = 0.0027), drug-related AEs (p = 0.015), and serious infections (p = 0.0006) than abatacept. It was not possible statistically to differentiate between infliximab and abatacept for any of the other secondary safety outcomes, although we cannot exclude the possibility that there are more autoimmune adverse events associated with abatacept (Table 3).

In comparisons of efficacy outcomes, abatacept is noninferior to adalimumab (i.e., abatacept is at least as good as adalimumab). There were no reasons to suspect any statistical differences between abatacept and adalimumab for any of the secondary safety outcomes (p ≥ 0.16). When network analysis was used to indirectly compare adalimumab with infliximab for the secondary efficacy outcomes, the analyses favored adalimumab; the only exceptions were ACR70 and DAS28 remission. Secondary safety outcomes also supported adalimumab over infliximab; the majority of outcomes indicated that infliximab was more likely than adalimumab to result in significant adverse effects.

Ancillary analyses

As a further goal from the evidence synthesis, we also examined *post hoc* (from the indirect part of the network) whether abatacept iv. and abatacept sc. were comparable for both our primary outcomes [31]. For the primary efficacy outcome, ACR50, equivalence was noted (OR: 0.97; 95% CI: 0.66–1.43; p = 0.88). The two drugs were also comparable with regards to the

Table 3. Summary of the findings of ATTEST-AMPLE network trial of selected biologics for rheumatoid arthritis.

Outcome	Abatacept vs adalimumab			Abatacept vs infliximab			Adalimumab vs infliximab†		
	OR	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Benefit									
ACR20	1.10	0.81–1.51	0.54	1.91	1.24–2.93	0.0032	1.73	1.04–2.87	0.034
ACR50	1.00	0.75–1.32	0.99	1.49	1.03–2.15	0.032	1.49	1.02–2.19	0.041
ACR70	1.11	0.81–1.52	0.52	1.52	0.99–2.33	0.055	1.37	0.87–2.15	0.17
LDAS (DAS28)‡	0.91	0.67–1.25	0.57	1.94	1.19–3.16	0.0079	2.12	1.19–3.78	0.011
Remission (DAS28)§	1.06	0.77–1.44	0.72	1.71	0.93–3.16	0.084	1.62	0.82–3.21	0.17
Harm									
Deaths	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.	n.e.
SAEs	1.09	0.68–1.77	0.72	0.50	0.30–0.81	0.0056	0.45	0.26–0.78	0.0044
Related SAEs	0.81	0.36–1.84	0.62	0.30	0.14–0.66	0.0027	0.37	0.17–0.84	0.018
Discontinuation due to SAEs	0.54	0.21–1.44	0.22	0.46	0.15–1.41	0.17	0.85	0.28–2.53	0.77
AEs	1.21	0.79–1.85	0.37	0.54	0.28–1.07	0.077	0.45	0.23–0.89	0.023
Related AEs	0.83	0.60–1.15	0.27	0.58	0.38–0.90	0.015	0.70	0.41–1.19	0.19
Discontinuation due to AEs	0.54	0.27–1.05	0.07	0.45	0.21–0.96	0.040	0.83	0.39–1.74	0.62
Serious infections	0.76	0.31–1.90	0.56	0.23	0.10–0.53	0.0006	0.30	0.13–0.72	0.0067
Autoimmune events	2.30	0.72–7.35	0.16	3.44	0.41–28.88	0.25	1.50	0.14–15.45	0.74

†*When indirectly comparing adalimumab with infliximab via the populations included in the ATTEST and AMPLE studies, they are different for some important prognostic factors, reducing our confidence in the estimates for these particular network comparisons.*
‡*DAS28-CRP score of ≤3.2.*
§*DAS28-CRP score of ≤2.6.*
ACR20: 20% response on the ACR improvement criteria; ACR50: 50% response on the ACR improvement criteria; ACR70: 70% response on the ACR improvement criteria; AE: Adverse event; DAS28: Disease activity score in 28 joints; LDAS: Low disease activity score; n.e.: Not estimable; OR: Odds ratio; SAE: Serious adverse event.

number of participants discontinuing owing to AEs (OR: 0.92; 95% CI: 0.32–2.71; p = 0.89).

Discussion

Compared with TNF inhibitors, abatacept is one of a group of medications that blocks the activity of T-cells, a type of immune cell in the body that causes swelling and joint damage in patients with RA [15,16]. Following the comparative effectiveness paradigm, we evaluated the relative efficacy and safety of abatacept compared with infliximab (iv.: 3 mg/kg every 8 weeks) and adalimumab (sc.: 40 mg administered every other week) [20,22]. Network analysis allowed indirect comparisons across all three groups, something not possible in the original trials. The network analysis demonstrated that infliximab at the recommended (although low) dose, is less efficacious than either adalimumab or abatacept, and that adalimumab and abatacept are approximately equivalent. Despite the lower dose of infliximab, this drug was associated with statistically more AEs than the other two drugs. In light of the increased focus AEs have been receiving, the risk–benefit ratio of infliximab – even at low dose – favors both abatacept and adalimumab.

Indirect evidence from Kristensen *et al.* demonstrates that adalimumab, etanercept, and infliximab are equally effective if infliximab is prescribed in the 'right' dose – probably corresponding to 3 mg/kg every 4 weeks [9]. Thus the findings of the ATTEST study could rightfully be criticized by infliximab advocates, as the dose applied is probably inadequate for a 1-year trial. From the study by Kristensen *et al.*, the expected absolute benefit of receiving adalimumab, etanercept and infliximab (double dose) corresponds to a number needed to treat of four patients according to ACR50 [9]. We would anticipate that an increased dose of infliximab, while being more effective would also imply an increased risk of AEs and subsequent withdrawals [32].

This analysis gives no indications that there is a clinically significant difference in the efficacy of abatacept compared with adalimumab in end point (Tables 2 & 3). The literature also gives no indication of a difference in onset of effect [22]. Our discontinuation for AE analysis showed no differences between the two drugs. In AMPLE, the only AEs that were different between these two drugs was in injection site reactions, which favored abatacept [22]. This small difference does

not allow one to clearly differentiate these drugs on a group basis. A choice as to which drug to use on an individual basis will be dependent on individual factors, such as concomitant illnesses [13] (e.g., hepatitis [33] and serious infections [34]).

Limitations

With only a few head-to-head comparison trials, indirect comparisons may be used to answer comparative efficacy issues (including network meta-analyses that combine information from trials in a connected network). Network meta-analyses apparently allow inferences regarding head-to-head comparisons, even when there is little or no head-to-head evidence, which rightfully can be considered a limitation of the methodology applied in this study [25].

Indirect comparisons build – at least to some extent – on the premise that the studies combined in the network are comparable. When comparing the populations included in the ATTEST and AMPLE study, they are different for some key prognostic factors. For instance, in the ATTEST study, the disease activity is greater than in the AMPLE study. Also, the mean disease duration in ATTEST study was longer than in the AMPLE study. In the AMPLE study many of the participants were from North America, while in the ATTEST study the majority of patients came from South America. These caveats are limitations, potentially reducing our confidence in the estimates when comparing adalimumab with infliximab.

Conclusion & future perspective

The core question of comparative effectiveness research is which treatment works best, for whom and under what circumstances. Currently it is not possible to predict, on an individual basis, which patients will respond to a particular therapy. In the absence of reliable biomarkers on which to base individual treatment decisions, current biological therapies all have relatively good efficacy in RA and target similar populations of patients [35]. The ATTEST–AMPLE network randomized trial strongly suggests that abatacept in combination with MTX is comparable to other biologic DMARDs (applied in the right dose) for the reduction of disease activity of RA in patients with active disease, despite previous treatment with MTX [10]. At present, the focus of clinicians may have to rest solely on clinical disease activity assessment and on rapidly targeting remission or low disease activity [36].

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Executive summary

Background

- Inflammation in patients presenting with rheumatoid arthritis should be suppressed as early as possible.
- During the last 10–20 years, highly effective disease-modifying biological agents have been developed.

Methods

- Combining direct and indirect data from two randomized trials in patients with rheumatoid arthritis and an inadequate response to methotrexate, we explored pros and cons for infliximab, adalimumab and abatacept.

Results

- Compared with infliximab, abatacept and adalimumab were associated with a higher likelihood of achieving a clinical response; response rates for abatacept and adalimumab were comparable.
- Abatacept and, indirectly, adalimumab were less likely than infliximab to result in adverse effects.

Conclusion

- Infliximab is less efficacious than abatacept; adalimumab and abatacept are approximately equivalent both in terms of benefit and harm.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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