Supplementary appendix S1

METHODS

Study population

Patients were observed in the Reade Rheumatology Registry (Dutch Trial Registry, number 6868) at the Amsterdam Rheumatology and immunology Center, location Reade. Patients had to have rheumatoid arthritis (RA) according to the American College of Rheumatology (ACR) criteria of 1987 or European League Against Rheumatism (EULAR)/ACR 2010. To receive a biological agent; treatment with at least two disease modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX), should have failed. Treatment allocation was at the discretion of the patients' treating rheumatologist. Patients were included between December 2004 and November 2012 and a proportion of patients from the registry are previously reported on (1, 2).

Patients received etanercept treatment as monotherapy or in combination with concomitant DMARD therapy or prednisone and this could be changed during the follow-up of the study by the treating rheumatologist. Discontinuation of biologic treatment was a decision of the treating rheumatologist and either due to failure or side effects. This study was performed in accordance with the ethical principles of the Declaration of Helsinki.

RESULTS

Patients

In total, 291 patients (65%) completed 52 weeks follow-up, of which 252 patients were biologic-naive and 39 patients were switcher. Regarding the switchers, median duration on previous adalimumab treatment was 45 weeks (interquartile range (IQR) 25-80) and most patients discontinued adalimumab treatment because of failure (n=49; 71%). The collected blood samples were taken 7 weeks (median; IQR 2-14) prior to treatment discontinuation.

Clinical response at week 52

Overall, switchers achieved less frequently simple disease activity index (SDAI) remission (n=10, 15%) compared to biologic- naive patients at week 52 (n=104, 27%, p=0.03). According to adalimumab concentration, 5/18 switchers (28%) with an adalimumab concentration <0.5 μg/mL, 1/18 (6%) with a concentration between 0.5-5.0 μg/mL and 3/27

(11%) with a concentration ≥5.0 μg/mL achieved SDAI remission (overall switcher-subgroups; p=0.13).

Switchers with an adalimumab concentration between 0.5-5.0 μg/mL and those with a concentration ≥5.0 μg/mL were less likely to achieve SDAI remission at week 52 compared to biologic-naive patients; respectively odds ratio (OR) 0.16 (95% confidence interval (CI) 0.02-1.19); p=0.07 and OR 0.33 (95% CI 0.10-1.13); p=0.08. Switchers with low adalimumab concentration had an OR comparable to biologic-naive patients; OR 1.02 (95% CI 0.36-2.93; p=0.97).

Mean improvement in disease activity score of 28 joints (DAS28) was significantly lower in switchers compared to biologic-naive patients after 52 weeks; 1.0 ± standard deviation (SD) 1.5 vs 1.6 ± 1.4; p<0.01. The change in DAS28 (ΔDAS28) was not significantly different between switchers with an adalimumab concentration <0.5 μg/mL (ΔDAS28 1.6 ± 1.6) and biologic-naive patients (ΔDAS28 1.6 ± 1.4; p=0.97) but was significant different for either switchers with an adalimumab concentration of between 0.5-5.0 μg/mL (ΔDAS28 0.5 ± 1.8; p<0.01) and ≥5.0 μg/mL (ΔDAS28 0.9 ± 1.2; p=0.1). The switcher-subgroups alone did not significantly differ (p=0.10).

Clinical response at week 28

EULAR good or moderate response criteria was achieved by 36 switchers (52%) and by 279 of the biologic-naive patients (73%; p<0.01) after 28 weeks of follow-up. Eleven out of 18 patients with adalimumab concentration <0.5 μg/mL (61%) achieved EULAR good or moderate response at 28 weeks and 9/18 (50%) and 12/27 (44%) of the patients with, respectively, concentrations between 0.5-5.0 μg/mL and ≥5.0 μg/mL (overall switcher-subgroups; p=0.36)**.**

Switchers with adalimumab concentrations between 0.5-5.0 μg/mL and ≥5.0 μg/mL were less likely to achieve EULAR good or moderate response compared to biologic-naive patients, respectively OR 0.38 (95% CI 0.14-1.00; p=0.05) and OR 0.29 (95% CI 0.13-0.64; p<0.1). The OR of patients with adalimumab concentrations <0.5 μg/mL was 0.73 (95% CI 0.25-2.17; p=0.58) compared to biologic- naive patients.

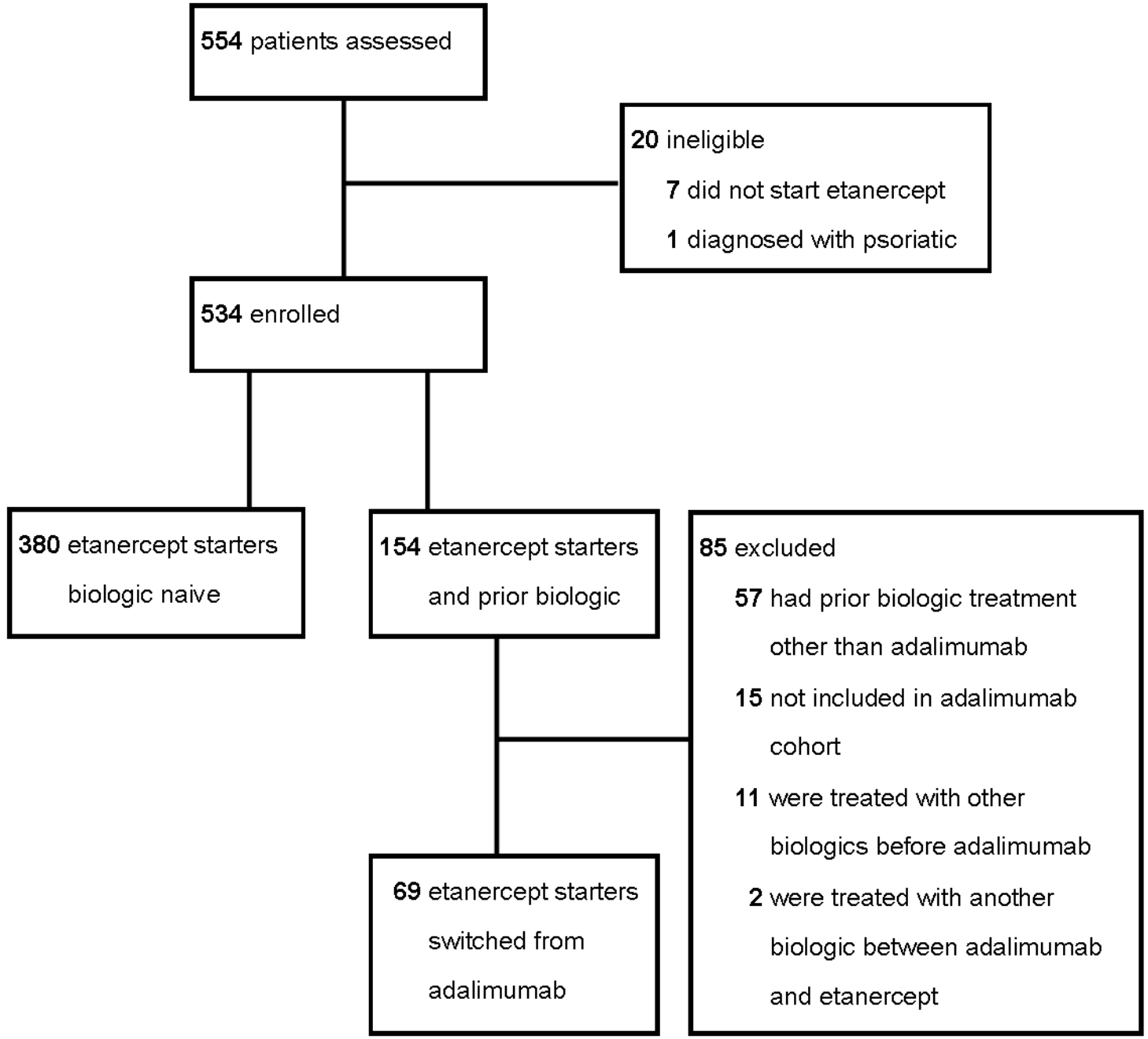
Switchers achieved less frequently SDAI remission (n=9, 13%) compared to biologic-naive patients (n=88, 23%; p=0.01) at week 28. Two out of 18 switchers (11%) with an adalimumab concentration <0.5 μg/mL, none of the switchers with a concentration between 0.5-5.0 μg/mL and 4/27 (15%) with a concentration ≥5.0 μg/mL achieved SDAI remission at week 28, (p=0.24).

Mean improvement in DAS28 was significantly lower in patients whom switched from adalimumab compared to biologic-naive patients after 28 weeks of treatment with etanercept: 1.0 ± 1.5 vs 1.7 ± 1.4 (p<0.01). Linear regression showed that switchers with concentrations <0.5 μg/mL (ΔDAS28 1.3 ± 1.5) did not significantly differ from biologic-naive patients (p=0.35). Switchers with an adalimumab concentration between 0.5-5.0 μg/mL (ΔDAS28 0.7 ± 1.7) and those with a concentration ≥5.0 μg/mL (ΔDAS28 0.8 ± 1.5) did significantly improve less in DAS28 compared to biologic-naive patients, both with p<0.01. The switcher-subgroups did not significantly differ from each other (p=0.46).

REFERENCES

1. Jamnitski A, Bartelds GM, Nurmohamed MT, van Schouwenburg PA, van SD, Stapel SO, et al. The presence or absence of antibodies to infliximab or adalimumab determines the outcome of switching to etanercept. Ann Rheum Dis. 2011;70:284-8.

2. Krieckaert CL, Jamnitski A, Nurmohamed MT, Kostense PJ, Boers M, Wolbink G. Comparison of long-term clinical outcome with etanercept treatment and adalimumab treatment of rheumatoid arthritis with respect to immunogenicity. Arthritis Rheum. 2012;64:3850-5.


554 patients assessed
20 ineligible
7 did not start etanercept
1 diagnosed with psoriatic
534 enrolled
380 etanercept starters
biologic naive
154 etanercept starters
and prior biologic
85 excluded
57 had prior biologic treatment
other than adalimumab
15 not included in adalimumab
cohort
11 were treated with other
biologics before adalimumab
2 were treated with another
biologic between adalimumab
and etanercept
69 etanercept starters
switched from
adalimumab