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ORIGINAL ARTICLE

Adalimumab combined with methotrexate versus adalimumab monotherapy in psoriasis: Three-year follow-up data of a single-blind randomized controlled trial

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Abstract

Background: Anti-drug antibodies (ADA) are formed in patients treated with adalimumab (ADL). This might increase clearance of ADL, potentially causing a (secondary) non-response. Combination therapy of ADL and methotrexate (MTX) reduces ADA levels and has a clinical benefit in rheumatologic diseases. In psoriasis however, the long-term effectiveness and safety have not been studied.

Objectives: To investigate the three-year follow-up data of ADL combined with MTX compared to ADL monotherapy in ADL-naive patients with moderate to severe plaque type psoriasis.

Methods: We conducted a multicentre RCT in the Netherlands and Belgium. Randomization was performed by a centralized online randomization service. Patients were seen every 12 weeks until week 145. Outcome assessors were blinded. We collected data on drug survival, effectiveness, safety, pharmacokinetics and immunogenicity of patients that started ADL combined with MTX compared to ADL monotherapy. We present descriptive analysis and patients were analysed according to the group initially randomized to. Patients becoming non-adherent to the biologic were excluded from analyses.

Results: Sixty-one patients were included and 37 patients (ADL group $n = 17$, ADL + MTX group $n = 20$) continued in the follow-up study after 1 year. After 109 weeks and 145 weeks, there was a trend towards longer drug survival in the ADL + MTX group compared to the ADL group (week 109: 54.8% vs. 41.4%; $p = 0.326$, week 145: 51.6% vs. 41.4%; $p = 0.464$). At week 145, 7/13 patients were treated with MTX. In the ADL group, 4/12 patients that completed the study developed ADA, and 3/13 in the ADL + MTX group.

Conclusions: In this small study, there was no significant difference in ADL overall drug survival when it was initially combined with MTX, compared to ADL alone. Discontinuation due to adverse events was common in the combination group. To secure accessible healthcare, combination treatment of ADL and MTX can be considered in individual patients.

INTRODUCTION

Adalimumab (ADL, TNF inhibitor) is a beneficial treatment option for many patients with chronic plaque psoriasis. During treatment with ADL however, anti-drug antibodies (ADA) are formed.[1–3] ADA impair the binding to target TNF and increase clearance of ADL. This results in lower levels of circulating ADL, which can potentially cause a (secondary) non-response. The formation of detectable ADA occurs in 0–51% of the patients according to different studies.[1,2,4,5] This varying percentage has several causes; detection methods have improved, resulting in increased reporting of immunogenicity.[6] Also, sample collection timing, study population characteristics or use of concomitant medication have an impact on ADA detection.[4]

In rheumatology patients, concomitant methotrexate (MTX) may be able to decrease the formation of ADA in ADL-treated patients.[7–10] In these studies, patients on combination therapy showed greater improvement of their rheumatic disease and their skin disease.[11,12]

In psoriasis, the effectiveness of the combination of MTX and ADL has been studied in a case series[13] and two observational cohort studies.[14,15] These studies showed differential outcomes; the addition of MTX to ADA increased treatment satisfaction, effectiveness and quality of life,[15] the combination with MTX led to a good or very good response in part of the patients[12] and the addition of MTX resulted in a better Psoriasis Area Severity Index (PASI) response in a subgroup of patients.[14]

Recently, we published the first-year results of a randomized controlled trial (RCT) in which we compared ADL with ADL + MTX treatment in psoriasis patients.[16] We found a trend towards a better overall drug survival in the ADL + MTX group after 1 year. In this group, significantly more patients achieved a PASI 75 at week 5 (22.6% vs 3.5%; $p = 0.05$). The median [IQR] serum trough concentrations (therapeutic range is 3.2–7 mg/L[17]) were numerically higher in the ADL + MTX group (6.8 [5.5–9.2]) versus ADL group (5.9 [3.5–8.8]; $p = 0.26$). In the ADL monotherapy group, more patients showed detectable ADA (ADL group 60% vs. ADL + MTX group 22.6%; $p < 0.01$).

Long term RCT data on the efficacy and safety of ADL monotherapy and ADL + MTX combination therapy in psoriasis is lacking.[11,13,14] Therefore, the objective of the follow-up study was to investigate the overall drug survival, effectiveness, safety, pharmacokinetics (PK) and immunogenicity of ADL combined with MTX compared to ADL monotherapy until 145 weeks of follow-up.

MATERIALS AND METHODS

Study design

This study presents the 3-year data of a pragmatic, single-blinded, investigator-initiated RCT.[18] The study is reported according to the CONSORT 2010 statement (Appendix S1).[19] The study has been performed in four academic centres (Amsterdam UMC, Radboud UMC, Erasmus, MC, UZ Ghent) and one non-academic hospital (Amphia Hospital). The protocol has been published previously.[18] The study was registered in the Netherlands National Trial Register (NTR4499).

Ethics statement

Ethical approval was obtained from the local medical ethics committee (NL47129.018.13), the EudraCT number was 2013–004918-18. Further details on the study design, randomization, blinding, study sample size calculation and selection criteria can be found in our previous papers.[16,18]

Study participants

Of the 114 patients screened between March 2014 and November 2017, 66 patients were randomized in the trial (33 patients in the ADL group and 33 patients in the ADL + MTX group).[16] Thirty-seven patients continued in the follow-up study after week 49. The last patient visit took place in June 2020. See also Figure 1.

Treatment regimens during the study

In the follow-up study, the ADL administration continued to be dosed according to label (40 mg every 2 weeks). MTX was dosed orally in 10 mg/week (or 7.5 mg/week in case of mild toxicity or intolerability), followed by 5 mg folic acid 24 hours after MTX administration. Due to the pragmatic design, it was allowed to interrupt the ADL treatment temporarily in the study (maximum of 2 weeks up to four times during the entire study) and to perform treatment changes, including the addition or discontinuation of methotrexate.

Data collection and blinding

Data were collected every 12 weeks until week 145. Investigator-reported outcomes (PASI and Investigator Global Assessment, IGA) were assessed by blinded and trained investigators. Together with the patient, the physician assessed the Adverse Events (AE), severity and relatedness to treatment.

Outcomes

Drug survival and effectiveness

The primary outcome of the RCT was the overall drug survival of ADL after week 49 (year 1). A secondary outcome was overall drug survival of ADL after week 109 (year 2) and week 145 (year 3). Other secondary outcomes were the mean change in PASI, percentage of patients achieving PASI 75 and PASI 90, proportion of patients achieving IGA 0/1 (Clear or Almost
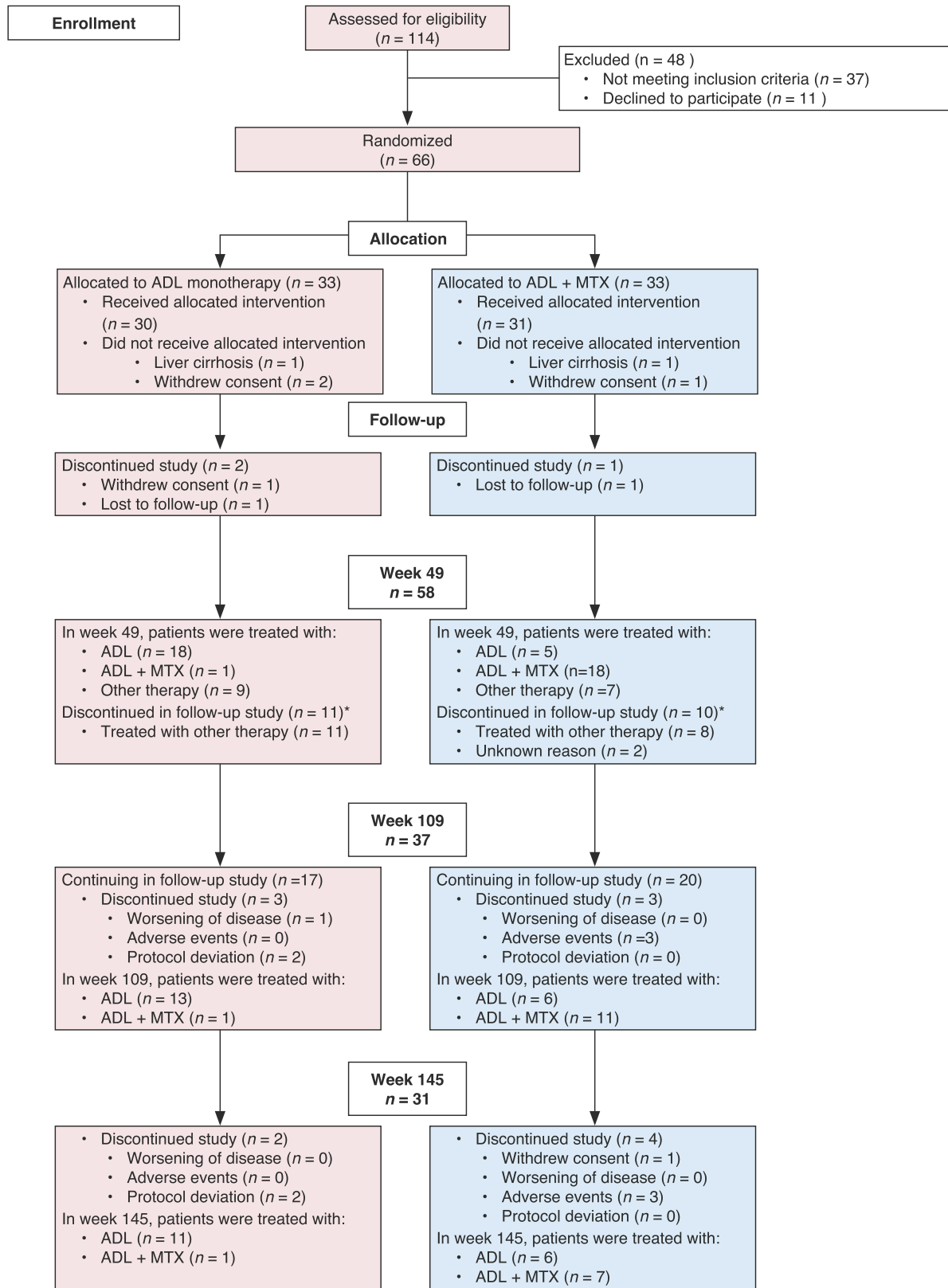
Enrollment

Assessed for eligibility
($n = 114$)

Excluded ($n = 48$)
- Not meeting inclusion criteria ($n = 37$)
- Declined to participate ($n = 11$)

Randomized
($n = 66$)

Allocation

Allocated to ADL monotherapy ($n = 33$)
- Received allocated intervention
  ($n = 30$)
- Did not receive allocated intervention
  - Liver cirrhosis ($n = 1$)
  - Withdrew consent ($n = 2$)

Allocated to ADL + MTX ($n = 33$)
- Received allocated intervention
  ($n = 31$)
- Did not receive allocated intervention
  - Liver cirrhosis ($n = 1$)
  - Withdrew consent ($n = 1$)

Follow-up

Discontinued study ($n = 2$)
- Withdrew consent ($n = 1$)
- Lost to follow-up ($n = 1$)

Discontinued study ($n = 1$)
- Lost to follow-up ($n = 1$)

Week 49
$n = 58$

In week 49, patients were treated with:
- ADL ($n = 18$)
- ADL + MTX ($n = 1$)
- Other therapy ($n = 9$)
Discontinued in follow-up study ($n = 11$)*
- Treated with other therapy ($n = 11$)

In week 49, patients were treated with:
- ADL ($n = 5$)
- ADL + MTX ($n = 18$)
- Other therapy ($n = 7$)
Discontinued in follow-up study ($n = 10$)*
- Treated with other therapy ($n = 8$)
- Unknown reason ($n = 2$)

Week 109
$n = 37$

Continuing in follow-up study ($n = 17$)
- Discontinued study ($n = 3$)
  - Worsening of disease ($n = 1$)
  - Adverse events ($n = 0$)
  - Protocol deviation ($n = 2$)
In week 109, patients were treated with:
- ADL ($n = 13$)
- ADL + MTX ($n = 1$)

Continuing in follow-up study ($n = 20$)
- Discontinued study ($n = 3$)
  - Worsening of disease ($n = 0$)
  - Adverse events ($n = 3$)
  - Protocol deviation ($n = 0$)
In week 109, patients were treated with:
- ADL ($n = 6$)
- ADL + MTX ($n = 11$)

Week 145
$n = 31$

- Discontinued study ($n = 2$)
  - Worsening of disease ($n = 0$)
  - Adverse events ($n = 0$)
  - Protocol deviation ($n = 2$)
In week 145, patients were treated with:
- ADL ($n = 11$)
- ADL + MTX ($n = 1$)

- Discontinued study ($n = 4$)
  - Withdrew consent ($n = 1$)
  - Worsening of disease ($n = 0$)
  - Adverse events ($n = 3$)
  - Protocol deviation ($n = 0$)
In week 145, patients were treated with:
- ADL ($n = 6$)
- ADL + MTX ($n = 7$)

FIGURE 1 Flow diagram of participation in the study per protocol after week 49, week 109 and week 145. ADL = Adalimumab, AE = Adverse Events, MTX = methotrexate, * = after week 49, patients that discontinued ADL for more than 2 weeks, were no longer followed.

Clear), Patient Global Assessment 0/1 (PGA, Clear or Almost Clear), mean change from baseline in Dermatology Life Quality Index (DLQI), mean change from baseline in Skindex-29, and the proportion of patients achieving the treatment goals of Mrowietz et al. (PASI ≥75 or PASI ≥50 < 75 and DLQI≤5).[20] All outcomes were assessed at week 109 and week 145.

PK

ADA and ADL serum trough levels were measured in order to gain insight into the PK aspects of ADL clearance in the context of ADA formation. The ADA titers and serum-through concentration were assessed by Sanquin laboratory (Amsterdam, the Netherlands) using a validated radioimmunoassay and a validated ELISA, respectively.[21–23] ADA titers <12 AU/mL were defined as no antibodies, ADA titers >12 AU/mL were defined as antibodies. Due to the low number of remaining patients, no further classification could be made. A serum trough level was significant if ≥3.2 µg/mL. See for more details our previous paper.[16]

Safety

Safety was measured trough laboratory analysis according to the Dutch psoriasis guideline.[24] The safety outcome measurements involved the number of patients with (serious) AEs, subdivided in MedDRA terms,[25] and specification of liver enzyme elevations.

Statistical analysis

Due to a small number of patients that completed the three-year follow-up period, the most data are analysed with descriptive statistics. Patients were analysed in their original treatment group, independent from the treatment receiving at that moment. To give insight in the characteristics of the patients that discontinued ADL during the initial and follow-up study, we decided to describe the outcomes of the patients on the moment of ADL discontinuation separately. The presented data are collected on the last visit before patients discontinued, varying from week 9 till week 121.

For drug survival we used a log rank test. In both treatment groups, the Kaplan–Meier method was used to evaluate the overall drug survival of ADL. The event was defined as discontinuation of ADL therapy, and drug survival was subdivided for patients that discontinued ADL due to ineffectiveness. Patients were censored when lost to follow-up or in case of protocol deviations (use of prohibited concomitant therapy or interruption of ADL for more than 2 weeks). We choose not to impute missing data, due to the small number of patients that completed the study.

Statistical analyses were performed using IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.

RESULTS

Thirty-seven patients participated in the follow-up study *after* week 49, 17 were originally randomized in the ADL group and 20 patients in the ADL + MTX group, see also Figure 1. Note that many patients in the ADL + MTX group

TABLE 1 Baseline Characteristics from patients per protocol participating in the study after week 49.

	ADL (*n* = 17)	ADL + MTX (*n* = 20)
Male sex (%)	10 (58.8%)	18 (90%)
Age at baseline, mean (SD)	45.9 (± 13.6)	49.5 (± 14.4)
Disease duration in years, median (IQR)	19.3 (5.3–33.3)	16.4 (2.3–30.5)
Diagnosed with PsA, *n* (%)	4 (23.5%)	5 (25%)
Weight, mean (SD)	83.76 kg (± 14.3)	79.44 kg (± 16.7)
BMI, kg/m², median (IQR)	26.7 (3.29)	25.1 (4.65)
Smoker, yes (%)	4 (23.5%)	8 (40%)
Alcohol, yes (%)	13 (76.4%)	14 (70%)
Biologic naïve, yes (%)	11 (68.7%)	11 (57.9%)
Previous MTX used	16 (94.1%)	18 (90%)
PASI, mean (SD)	11.3 (± 3.1)	15.3 (± 6.8)
IGA		
Clear	0 (0%)	0 (0%)
Almost clear	0 (0%)	0 (0%)
Mild	0 (0%)	2 (10%)
Moderate	12 (70.6%)	8 (40%)
Severe	5 (29.4%)	10 (50%)
PGA		
Clear	0 (0%)	0 (0%)
Almost clear	0 (0%)	1 (5.3%)
Mild	1 (5.9%)	1 (5.3%)
Moderate	9 (52.9%)	5 (26.3%)
Severe	7 (41.2%)	12 (63.2%)~
DLQI, mean	10.1 (± 5.9)	13.5 (± 7.3)
Skindex-29, mean	42.3 (± 21.7)	52.2 (± 25.8)

Abbreviations: ADL, adalimumab; BMI, Body Mass Index; DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; IQR, Interquartile range; MTX, methotrexate; PASI, Psoriasis.

discontinued MTX during the study. At week 134, 7/13 patients did still use ADL + MTX.

The baseline characteristics and demographics of the patients that participated in the study after week 49 are shown in Table 1. Differences between the two treatment groups were: the number of male patients and mean PASI at baseline. These differences were absent at baseline in the original RCT.[16] However, the clinically relevant difference in BMI reported in the original RCT,[16] was not found in the patients continuing in the follow-up study.

Drug survival

The ADL overall drug survival curves can be found in Figure 2a. Compared to the monotherapy group, a tendency towards better drug survival was found for the combination group (week 109: 54.8% vs. 41.4%; *p* = 0.326, week 145: 51.6% vs. 41.4%; *p* = 0.464). The ADL drug survival was also

calculated for patients that discontinued the study due to ineffectiveness (Figure 2b). This drug survival was significantly better for the combination group (week 109: 93.5% vs. 73.3% $p = 0.04$, week 145: 90.1% vs. 66.7% $p = 0.03$).

Effectiveness

In Table 2 all descriptive analyses are presented after week 109 and week 145 in patients that continued ADL > 49 weeks. This number of patients is different from the flowchart in Figure 1. We presented all patients for which data were available (extra patients on week 109; ADL $n = 2$, ADL + MTX $n = 0$, on week 145; ADL $n = 3$, ADL + MTX $n = 2$). These patients were not treated per protocol, due to the start of extra MTX before week 49 ($n = 1$), discontinuation of ADL for more than 2 weeks due to tooth surgery ($n = 2$) and change of ADL frequency ($n = 2$). We decided to include them in our effectiveness analysis, due to the small remaining number of patients and the pragmatic setting of this trial. Data of the different patient groups were analysed in their original treatment group.

For the ADL and ADL + MTX group, the median PASI score reduction was 8.2 (6.1–10.3) versus 11.0 (8.4–16.3) after week 109 and 8.5 (5.1–10.2) versus 11.9 (6.9–17.6) after week 145. In the ADL group 50% (8/16) achieved a PASI 75 compared to 82.3% (14/17) in the ADL + MTX group at week 109. After week 145, 60% (9/15) achieved a PASI 75 response in the ADL group and 64.3% (9/14) in the ADL + MTX group.

For patients that discontinued the study, see Table 3. In the ADL group, 31.2% achieved a PASI 75 compared to 50% in the ADL + MTX group.
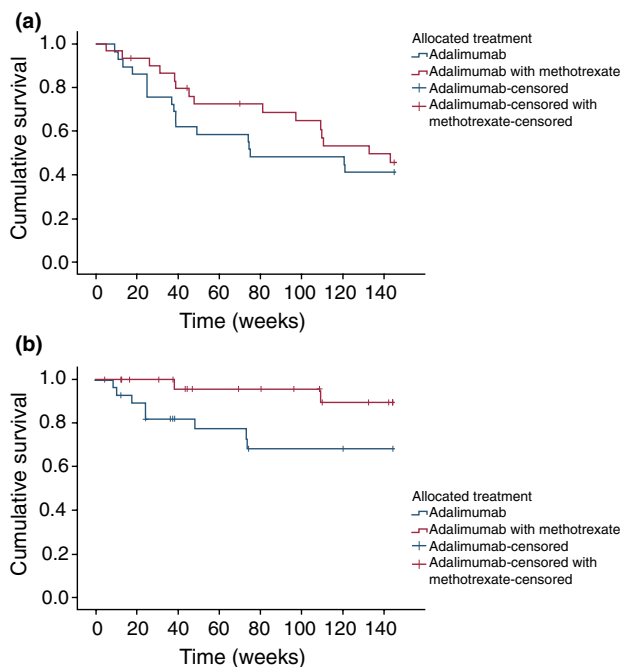
FIGURE 2 (a) Adalimumab drug survival. (b) Adalimumab drug survival for patients that discontinued adalimumab due to ineffectiveness.

Quality of life

In Table 2 the improvement of the quality of life is presented. The mean DLQI reduction at week 109 was 8.8 (±6.5) in the ADL group and 10.4 (±7.41) in the ADL + MTX group. The reduction in the Skindex-29 score at week 109 was 27.5 (±18.2) in the ADL group and 32.4 (±23.3) in the ADL + MTX group. At week 145 the Skindex-29 score reduction was 32.5 (±20.1) in the ADL group and 33.2 (±27.7) in the ADL + MTX group.

The data involving the patients that discontinued the study (Table 3), 7.4 (±7.0) in the ADL group and 6.9 (±7.4) in the ADL + MTX group, are comparable for the DLQI reduction for the patients that completed week 109 and week 145 (Table 2). The Skindex-29 reduction in the group that discontinued the study is lower compared to this reduction at week 109 and week 145 (22.5 vs. 25.2 for the ADL group and ADL + MTX group, respectively).

PK

In Figure 3 the PK endpoints can be found.

In the ADL group, four out of 12 patients that continued the study after week 49 and also completed the total follow-up, showed ADA at any given time-point in the study. Three patients started with MTX. One of them kept sufficient ADL serum trough levels, but the other patient had a temporary lower serum trough level (from week 37 till week 85) and sufficient serum trough levels on the other time points. The third patient showed ADA until week 109. After the start of MTX on that visit date, no further ADA were detected and the serum trough levels were back to ≥3.2. The fourth patient showed ADA on two different time points in the study, but with sufficient serum levels.

In the ADL + MTX group, three out of 13 patients that continued the study after week 49 and completed the total follow-up, showed ADA at any given time-point. One patient showed intermittent ADA formation, with insufficient serum trough levels. Another patient showed ADA with insufficient serum trough levels after the cessation of MTX. A patient in the ADL + MTX group, stopped MTX treatment on week 73 and developed ADA on week 133 and week 145. On those time points the ADL serum trough levels were below 3.2.

For patients that discontinued, see Table 3. The number of patients with ADA during the last patient visit in the ADL + MTX group is lower than in the ADL group. A comparable result is found for the number of patients with serum trough levels below the therapeutic range.

Safety

In Table 4, all AEs and SAEs occurring in the study can be found. Of the total AEs, we found an observation rate of 357 AE/100 patient years (CI 292–1299) in the ADL group and 391 AE/100 patient years (CI 278–1235) in the ADL + MTX

TABLE 2 Descriptive analyses for clinical response at week 109 and week 145 in patients continuing ADL after week 49.

Week 109	ADL group (n = 16)±	ADL + MTX group (n = 17)±
Primary outcome		
ADL overall drug survival, %	41.4	54.8
Secondary outcomes		
ADL ineffectiveness drug survival, %	73.3	93.5
Δ PASI score, median (IQR)	−8.2 (−6.1; −10.3)	−11.0 (−8.4; −16.3)
PASI 75, % (n/total)	50 (8/16)	82.3 (14/17)
PASI 90, % (n/total)	37.5 (6/16)	41.2 (7/17)
IGA 0/1, % (n/total)	68.8 (11/16)	47.1 (8/17)
PGA 0/1, % (n/total)	93.8 (15/16)	81.3 (13/16)[a]
Δ DLQI score, mean (SD)	−8.8 (±6.5)	−10.4 (±7.41)
Δ Skindex-29, mean (SD)	−27.5 (±18.2)	−32.4 (±23.3)
Treatment goals[b], % achieved	81.3 (13/16)	88.2 (15/17)
Week 145	**ADL group (n = 15)±**	**ADL + MTX group (n = 15)±**
Primary outcome		
ADL drug survival	41.4	51.6
Secondary outcomes		
ADL ineffectiveness drug survival, %	66.7	90.1
Δ PASI score, median (IQR)	−8.5 (−5.1; −10.2)	−11.9 (−6.9; −17.555)
PASI 75, % (n/total)	60 (9/15)	64.3 (9/14)[a]
PASI 90, % (n/total)	40 (6/15)	50 (7/14)[a]
IGA 0/1, % (n/total)	53.3 (8/15)	53.3 (8/15)
PGA 0/1, % (n/total)	86.7 (13/15)	73.3 (11/15)
Δ DLQI score, mean (SD)	−9.7 (±6.2)	−10.3 (±8.2)
Δ Skindex-29, mean (SD)	−32.5 (±20.1)	−33.2 (±27.7)
Treatment goals[b], % achieved	85.7 (12/14)[a]	85.7 (12/14)[a]

Note: ± For drug survival analysis original number of patients was used; ADL = 30 patients, ADL + MTX = 31 patients.

Abbreviations: ADL, Adalimumab; IGA, Investigator Global Assessment; PASI, Psoriasis Area Severity Index; PGA, Patient Global Assessment.

[a]Missing data for one patient.

[b]Treatment goals according to Mrowietz et al.[20] PASI ≥75 or PASI ≥50 < 75 and DLQI ≤5.

group. Four SAEs occurred during the study; 1 SAE in the ADL group and 3 SAEs in the ADL + MTX group. Three SAEs involved surgeries; one elective meniscus surgery and one hemi-thyroidectomy in the ADL + MTX group, and one cyst lithotripsy/urethrectomy in the monotherapy group. The fourth SAE was reported in the ADL + MTX group and involved death due to a cerebrovascular accident. The patient had hypercholesterolemia as comorbidity. The data-safety monitoring board attributed all four SAEs unrelated to the intervention.

DISCUSSION

To our knowledge, this is the first long-term follow-up study in which effectiveness, safety, PK, immunogenicity and drug survival of ADL and ADL + MTX are compared in patients with psoriasis.

We found a trend towards a better drug survival for the ADL + MTX treatment group, though this difference was not significant. For patients that continued ADL for >49 weeks, the number of patients that achieved PASI 75 or developed ADA after 145 weeks, was almost equal. Besides, many patients in the ADL + MTX group experienced adverse events and therefore, stopped ADL or MTX. At week 145, only 7/13 patients were treated with MTX.

As in our previous publication, the overall ADL drug survival on week 109 and week 145 was comparable to the ADL drug survival on the same time points in the study of Egeberg et al.[26] From a RCT in children with Crohn's disease we know that the combination of ADL and an immunomodulatory treatment (azathioprine, 6-mercaptopurine or MTX) was not more effective than ADL monotherapy.[27] On the contrary, in rheumatoid arthritis, the combination of ADL and MTX treatment is quite common and shows more effective treatment outcomes.[7–10] This difference might be a

TABLE 3 Descriptive analyses for all patients that discontinued ADL in the study from week 0 till week 145, measured on the last patient visit before discontinuation.

	ADL group (n = 18)	ADL + MTX group (n = 18)
Reasons ADL discontinuation		
Adverse events	22.2% (4/18)	66.7% (12/18)
Ineffectiveness	38.9% (7/18)	0% (0/18)
Protocol deviation	27.8% (5/18)	0% (0/18)
Withdrew consent	0.06% (1/18)	0.06% (1/18)
LTFU	0.06% (1/18)	0.06% (1/18)
Reason unknown and other	0% (0/18)	22.2% (4/18)
Median ADL survival time (IQR)	37.50 (23.15; 74.04)	44.69 (23.79; 100.11)
Δ PASI score, median (IQR)	−7.75 (−1.48; −11.55)	−7.15 (−2.47; −11.97)
PASI 75, % (n/total)	31.2% (5/16)[a]	50% (9/18)
PASI 90, % (n/total)	12.5% (2/16)[a]	16.7% (3/18)
IGA 0/1, % (n/total)	22.2% (4/18)	38.9% (7/18)
PGA 0/1, % (n/total)	27.8% (5/18)	50% (9/18)
Δ DLQI score, mean (SD)	−7.4 (±7.0)	−6.9 (±7.4)
Δ Skindex-29, mean (SD)	−22.5 (±23.0)	−25.2 (±22.4)
ADA, yes, %	55.6% (10/18)	22.2% (4/18)
Serum trough levels, below <3.2 mg/L, %	61.1% (11/18)	27.8% (5/18)

Note: ± Other reasons; suspected interaction with pre-existent B cell lymphocytosis, reason unknown, fear of side effects.

Abbreviations: ADL, Adalimumab; IGA, Investigator Global Assessment; PASI, Psoriasis Area Severity Index; PGA, Patient Global Assessment.

[a]Missing data for two patients.
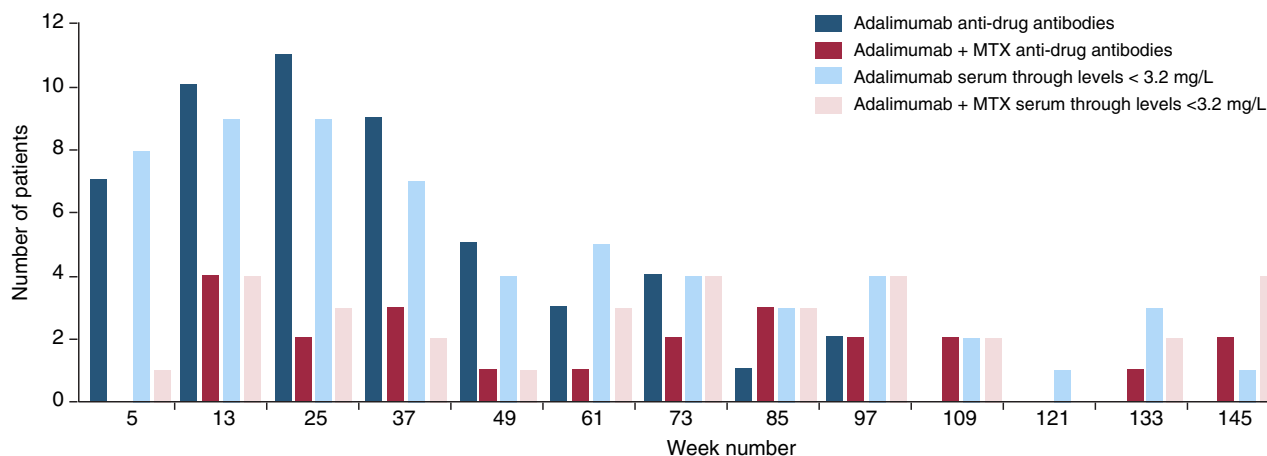
FIGURE 3 Anti-drug antibodies and serum trough levels. Number of patients with detectable anti-drug antibodies (ADA titers <12 AU/mL were defined as no antibodies, ADA titers >12 AU/mL were defined as antibodies) and serum trough levels <3.2 μg/mL per visit.

consequence of our small patient cohort, MTX dosing[7] or the different pathophysiology of the diseases.

During the first year of this RCT, no SAEs occurred.[16] Four SAEs (ADL + MTX n = 3, ADL n = 1) that were unrelated to treatment were reported between week 49 and week 145. Most AEs were respiratory infections or liver enzyme elevations. During year 2 and 3, 6 patients (19.3%) dropped-out of the study due to adverse events in the ADL + MTX group versus none in the ADL group. Two of those patients reported AEs that deemed to be related to MTX treatment;

neuropathy and monoclonal B cell lymphocytosis. Based on our results, addition of MTX to ADL therapy, may lead to more adverse events as a consequence.

In our study, patients developed ADA on different time points, both in the ADL group and ADL + MTX group. The patients with ADA had lower serum trough levels as well. These observations are in line with our hypothesis that ADA lowers the serum trough level of ADL and MTX appears to lower the formation of ADA. This is confirmed by the study from Papp et al.[15] in which the addition of MTX to ADL

TABLE 4   Adverse events from start study.

	ADL group (n = 30)[a]	ADL + MTX group (n = 31)[b]
Total numbers of adverse events	199 (46.5[c])	229 (53.5[c])
Serious adverse events	1 (3)	3 (9.7)
Severity of adverse event		
Mild	125 (62.8)	132 (51.4)
Moderate	62 (31.2)	76 (33.2)
Extreme	0 (0)	1 (0.4)
Death	1 (0.3)	0 (0)
Unknown	5 (2.5)	13 (5.7)
AE at least possibly related to study drug(s)	109 (54.8)	133 (55.0)
Action MTX or ADL treatment on adverse event	27 (42.2[c])	37 (57.8[c])
Treatment adjusted	16 (59.3)	20 (54.1)
Treatment stopped	11 (40.7)	17 (45.9)
Cardiac disorders	6 (3.0)	0 (0)
Ear and labyrinth disorders	1 (0.5)	0 (0)
Endocrine disorders	2 (1.0)	0 (0)
Eye disorders	0 (0)	2 (0.9)
Gastro intestinal disorders	13 (6.5)	21 (9.2)
General and administration site conditions	15 (7.5)	19 (8.3)
Hepatobiliary disorders	3 (1.5)	13 (5.7)
Immune system disorders	1 (0.5)	0 (0)
Infectious and infestations AE	55 (27.6)[d]	69 (30.1)[d]
Opportunistic infection	1 (0.5)	0 (0)
Respiratory thoracic mediastinal infection	23 (11.6)	12 (5.2)
Skin infection	12 (6.0)	23 (10.1)
Gastrointestinal infection	8 (4.0)	16 (7.0)
General e.g. influenza infection	8 (4.0)	16 (7.0)
Renal and urinary infection	4 (2.0)	2 (0.9)
Ear and labyrinth infection	2 (1.0)	7 (3.1)
Neoplasms e.g. genital warts infection	0 (0)	1 (0.4)
Ocular infection	0 (0)	4 (1.7)
Reproductive systems infection	1 (0.5)	1 (0.4)
Metabolism and nutrition disorders	2 (0.5)	2 (0.5)
Musculoskeletal and connective tissue disorders	24 (12.1)	29 (12.7)
Neoplasms, benign, malignant and unspecified[e]	0 (0)	3 (1.3)
Nervous system disorders	23 (11.6)	21 (9.2)
Psychiatric disorders	2 (1.0)	4 (1.7)
Renal urinary disorders	10 (5.0)	6 (2.6)
Reproductive system and breast disorders	4 (2.0)	0 (0)

TABLE 4   (Continued)

	ADL group (n = 30)[a]	ADL + MTX group (n = 31)[b]
Respiratory thoracic and mediastinal disorders	4 (2.0)	7 (3.1)
Skin and subcutaneous disorders	24 (12.1)	21 (9.2)
Surgical and medical procedures	4 (2.0)	6 (2.6)
Vascular disorders	6 (3.0)	4 (1.7)
Headache[f]	9 (4.5)	9 (3.9)
Fatigue[f]	6 (3.0)	12 (2.8)
Liver enzymes elevation[f]	42 (21)	32 (14.08)
>ULN	14 (7.0)	18 (7.9)
>2× ULN	2 (1.0)	3 (1.3)

Note: Data displayed as *n* (%), terminology based on MedDRA version 24.0 September 2021.[25]

Abbreviations: ADL + MTX group, adalimumab and methotrexate group; ADL-group, adalimumab group; AE, Adverse event; SAE, Serious adverse event; ULN, Upper limit of normal.

[a]Observation duration = 55.6 patient years.
[b]Observation duration = 58.5 patient years.
[c]Percentage of total number of AEs.
[d]Not all infections could be divided in a HLGT.
[e]Basal cell carcinoma was reported in one patient in the ADL + MTX group.
[f]This is no official MedDRA High Level Group Term (HLGT).

treatment increased treatment satisfaction, effectiveness and quality of life in psoriasis patients.

Strengths and limitations

A strength of the study design is the blinding of allocation and outcome assessors for the physician-reported outcomes. Another strength is the consequent interval of 12 weeks, which did not change during the follow-up study, making detection bias limited.

Due to ADL discontinuation, a large group of patients did not complete the three-year follow-up. Since the intention-to-treat analyses were not suitable for the remaining number of patients, we had to present descriptive data of a small group. Besides, their baseline characteristics showed significant differences; in the ADL group the number of male patients and the mean PASI score were lower.

Due to the small patient groups, our pragmatic design and the possibility to start or switch MTX between week 49 and week 145 of treatment, data of these patients should be interpreted cautiously.

In the ADL and ADL + MTX group, the number of patients achieving PASI 75, IGA 0/1, PGA 0/1 after 145 weeks, was almost equivalent. The mean DLQI and Skindex-29 reductions were in the same range and over 80% of the patients achieved the treatment goals.[20] This can be a consequence of the fact that patients with high PASI scores did not enter the follow-up period due to cessation of their ADL treatment in the first part of the study (before week 49) or due to a protocol deviation, e.g. by the use of prohibited high potency topical steroids.

Clinical implication and future perspectives

Although only one patient received a biosimilar temporarily, we think our results can be applied to other biosimilars[28] of ADL as well. Due to their availability, ADL and MTX are relatively affordable treatment options in an era with many different treatments for psoriasis.[29] Our results suggest a trend towards a better drug survival and effectiveness when ADL is at least initially combined with low dose MTX. However in the combination group, many patients discontinued MTX ($n = 6$) or ADL treatment ($n = 12$) due to adverse events. Besides, compared to ustekinumab and secukinumab,[30,31] even for ADL combined with MTX the drug survival is still quite low.

We believe that ADL treatment should be tailored to personal needs. In a population where TNF inhibitors should be started -e.g. due to comorbidities, for financial reasons, related to availability or insufficient effect of MTX alone- the combination of MTX to ADL might lead to better effectiveness and a longer drug survival. Other treatment strategies of these two drugs are of importance as well. MTX could, for example, be combined with ADL for the first 6 months and then cessed to prevent discontinuation due to AEs. Further research focusing on the effectiveness and safety of this treatment combination in a large cohort is of importance for biological treatment in psoriasis patients.

DATA AVAILABILITY STATEMENT
Individual patient data that underlie the results reported in this article are available on request. Data will be shared with researchers who provide a methodologically sound proposal after execution of a data-sharing agreement.

ETHICS STATEMENT
Ethical approval was obtained from the local medical ethics committee (NL47129.018.13), the EudraCT number was 2013–004918-18.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.