Detailed Long-term Dynamics of Neutrophil-to-Lymphocyte Ratio under Biologic Treatment Reveal Differential Effects of Tumour Necrosis Factor-alpha and Interleukin 12/23 Antagonists

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Psoriasis is thought to be associated with a reduced life expectancy through systemic inflammation. A comparative, retrospective analysis of neutrophil-to-lymphocyte ratio, a biomarker of systemic inflammation and cardiovascular risk, under 196 treatments with tumour necrosis factor-α and interleukin-12/23 antagonists was performed. Neutrophil-to-lymphocyte ratio decreased significantly within 3 months of initiation of treatment and remained stable at reduced levels for at least 33 months. Dynamics were more pronounced and neutrophil-to-lymphocyte ratio under treatment was lower in patients treated with tumour necrosis factor-α compared with interleukin-12/23 antagonists (geometric mean (95% confidence interval): 2.03 (1.9, 2.1) vs 2.63 (2.2, 3.2), respectively, $p = 0.014$). Tumour necrosis factor-α antagonist treatment and baseline neutrophil-to-lymphocyte ratio were independent predictors of a median low cardiovascular risk neutrophil-to-lymphocyte ratio (< 2.15) during treatment (odds ratio (95% confidence interval): 0.53 (0.4–0.8) and 4.68 (1.0–19.1), $p = 0.001$ and $p = 0.032$, respectively). These results demonstrate a rapid and sustained reduction in biomarkers of systemic inflammation under biologic treatment. Furthermore, these data suggest class-specific effects on systemic inflammation, which may be relevant for the prevention of psoriasis co-morbidity by systemic treatment.

Key words: psoriasis; adalimumab; etanercept; ustekinumab; biomarker; cardiovascular disease.

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SIGNIFICANCE

Psoriasis is thought to be associated with a reduced life expectancy through systemic inflammation. Analysis of neutrophil-to-lymphocyte ratio, which is a biomarker of systemic inflammation and cardiovascular risk, under 196 treatments with biologicals from 2 different classes was performed. While biologicals from both classes reduced the neutrophil-to-lymphocyte ratio, the effects were more pronounced under treatment with tumour necrosis factor-α compared with interleukin-12/23 antagonists. The reduction and prevention of systemic comorbidity is an emerging field in psoriasis treatment. These results support class-specific differences in the effects of biologicals on systemic inflammation, which may be relevant for treatment decisions.

Psoriasis is a chronic inflammatory disease associated with a loss of 5–20 life years in patients with severe and early-onset disease (1–4). Mounting evidence links key co-morbidities, such as cardiovascular disease and depression (5), with psoriasis via systemic inflammation, in what has been coined a "psoriatic march" (6). While, overall, biologics are thought to ameliorate systemic inflammation and cardiovascular risk (1, 7), heterogeneous data exist on respective biologic class effects, in particular among tumour necrosis factor-α (TNF-α) and interleukin (IL)-12/23 antagonists (8–10). Given the evolving focus on the prevention of psoriasis co-morbidities (11), further investigation of these differential effects is necessary.

Neutrophil-to-lymphocyte ratio (NLR) is a biomarker of systemic inflammation and an independent cardiovascular risk factor (12). NLR is elevated and may predict subclinical atherosclerosis in patients with psoriasis (13), but, interestingly, shows no significant correlation with Psoriasis Area and Severity Index (PASI) (14). To date, only very little comparative short-term data are available on the dynamics of NLR under different biologic treatments (15, 16).

A comparative retrospective analysis of real-world, long-term NLR dynamics under 196 treatment cycles with the TNF-α antagonists adalimumab ($n = 112$) and etanercept ($n = 61$), and the IL-12/23 antagonist ustekinumab ($n = 23$) for psoriasis was performed.

MATERIALS AND METHODS

Patients were eligible for study participation if: they were treated for psoriasis with adalimumab, etanercept or ustekinumab at the department of dermatology of the University of Heidelberg; gave informed consent; and 1 or more NLR values were available. A total of 196 treatment cycles from 143 patients were found to be eligible. Forty-four patients contributed data regarding more than 1 biologic. Patient characteristics and baseline parameters reflect the situation prior to initiation of the treatment cycle under investigation. The study was approved by the local ethics comittee of the University of Heidelberg.

Biologics are generally administered according to national guideline recommendations at our institution. A complete blood count is usually performed at baseline and subsequent clinical visits.

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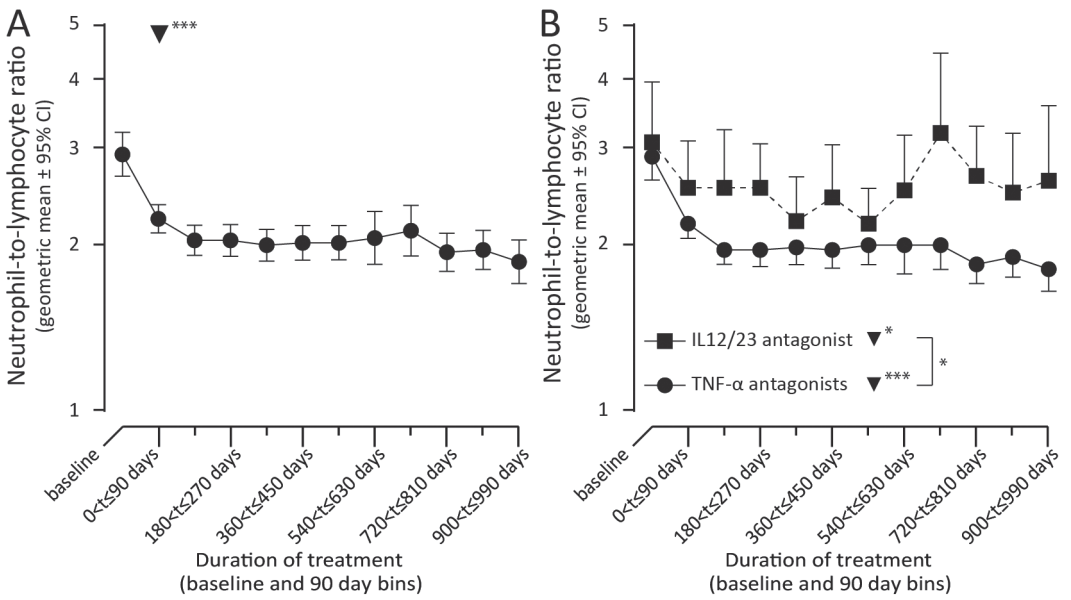

Fig. 1. Neutrophil-to-lymphocyte ratio (NLR) dynamics in patients treated for psoriasis with adalimumab or ustekinumab. (A) Dynamics of NLR under treatment with either of the biologics at baseline and during treatment, the latter binned over 90-day intervals (geometric mean and 95% confidence interval (gmean ± 95% CI). NLR decreased significantly from baseline to median under treatment (Student's paired *t*-test). (B) Dynamics of NLR under treatment with adalimumab (*circles, solid line*) or ustekinumab (*rectangles, dashed line*) shown separately at baseline and during treatment, the latter binned over 90-day intervals (gmean ± 95% CI). NLR decreased significantly from baseline to median under treatment with each of the biologics (Student's paired *t*-test). The median NLR under treatment was significantly lower in patients treated with adalimumab compared with ustekinumab (Student's *t*-test). Significant parameter dynamics during treatment are indicated by $*p<0.05$, $**p<0.01$, and $***p<0.001$, respectively, with an *arrowhead* depicting an increase (▲) or decrease (▼).

Baseline and median NLR under treatment (over the entire treatment duration) were calculated for each patient individually as robust statistical measures. NLR values were left skewed in the study population and had to be logarithmically transformed to satisfy the assumption of normality for Student's *t*-testing (Fig. S1[1]). As recommended for lognormally distributed parameters (17), NLR values are reported as geometric mean and 95% confidence interval (gmean (CI)), if not stated otherwise. For reference, mean and median values of the data shown in **Fig. 1**a are presented in Table SI[1]. Ninety-day bins were used for visualization in Fig. 1. Statistical tests were 2-sided and are detailed in the results section. $p<0.05$ was considered significant. Statistical procedures were performed using SPSS 22.0 (IBM, New York, NY, USA) and Microsoft Excel 2013 (Microsoft, Redmond, WA, USA).

RESULTS

Patient characteristics are shown in **Table I**. Overall, 2,365 NLR measurements were available from 335 treatment years, translating to 1 NLR measurement every 7.4 weeks on average. Fig. 1a shows that NLR decreased rapidly within the first 3 months of treatment (baseline 2.92 (2.7, 3.2) to 2.23 (2.1, 2.4)) and that significantly lower levels were sustained throughout the following treatment years (baseline vs median under treatment: 2.91 (2.7, 3.2) vs 2.09 (2.0,2.2), $p<0.001$, $n=168$, Student's paired *t*-test; cf. Fig. 1a and Table SI[1] for confidence intervals of individual bins). Table SI[1] provides measures of central tendency and number of patients for Fig. 1. The Spearman's rank correlation between treatment duration and NLR was significant within the first 120 days, but not at later time-points (baseline to 120 days and after 120 days, $r_s=-0.204$ and -0.039, $n=712$ and 1,653, $p<0.001$ and 0.109, respectively).

Fig. 1b compares NLR dynamics between patients treated with TNF-α antagonists (*circles, solid line*) and ustekinumab (*rectangles, dashed line*). While NLR decreased significantly under treatment in both groups (baseline vs median under treatment: $n=147$ and 21, $p<0.001$ and $p=0.039$, respectively, Student's paired t-test), the median NLR over the entire treatment duration was significantly lower in patients treated with TNF-α antagonists compared with ustekinumab (2.03 (1.9, 2.1) and 2.63 (2.2, 3.2), $n=172$ and 23, respectively, $p=0.014$; Student's *t*-test). Likewise, the reduction from baseline to median

Table I. Overall patients' characteristics

Patients' characteristics	
Number of treatments, *n*	196
Age, years, mean ± SD	47.3 ± 12
Sex, female, %	36
Psoriasis arthritis present, %	45
Number of previous systemic treatments mean ± SD	2.9 ± 2
Median [IQR]	3.0 [2.4]
Concomitant methotrexate, %	13
Biologic, %	
Adalimumab	57
Etanercept	31
Ustekinumab	12
Baseline Psoriasis Area and Severity Index, mean ± SD (*n*)	10.3 ± 7 (183)
Median [IQR]	9.3 [5, 14]
Baseline Neutrophil-to-lymphocyte ratio, gmean [SD] (*n*)	2.9 [2, 5] (169)
Median [IQR]	2.7 [2, 4]
Treatment duration, months, mean ± SD	21 ± 19

SD: standard deviation: IQR: interquartile range; gmean: geometric mean.

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NLR under treatment was significantly more pronounced under TNF-α compared with IL-12/23 antagonist treatment (–30.2% (–36, –24) and –12.3% (–22, –1), $n=147$ and 21, respectively, $p=0.044$, Student's t-test). There were no significant differences between the median PASI under treatment with TNF-α and IL12/23 antagonists (median ± interquartile range: 2.9 (1.2, 6.3) and 3.00 (1.5, 6.6), $n=161$ and 22, respectively, $p=0.710$, Mann–Whitney U test) or the median NLR under treatment with adalimumab and etanercept (2.06 (1.9, 2.2) and 1.96 (1.8, 2.1), $n=112$ and 60, respectively, $p=0.409$, Student's t-test).

No treatment goals exist for biomarkers of systemic inflammation in psoriasis. Recently, a study using data from the Jackson Heart Study found that an NLR ≥2.15 was significantly associated with an increased risk of all-cause mortality and coronary heart disease (hazard ratios 1.4 and 1.69, respectively) (18). The baseline NLR in the current study population was ≥2.15 in 67.5% (114 of 169) of the patients. **Table II** details characteristics of patients who had a baseline NLR of ≥2.15 ($n=114$) and did (40%) or did not (60%) reach a median NLR below 2.15 during treatment. Furthermore, the results of a multivariate logistic regression analysis to identify predictors for a reduction in the median NLR below 2.15 under treatment are presented. In the final model (stepwise backward, likelihood ratio method), patients with a high baseline NLR were less likely, and patients treated with TNF-α antagonists were more likely to reach a median NLR below 2.15 over the entire treatment period (odds ratio (95% CI): 0.53 (0.4–0.8) and 4.68 (1.0–19.1), $p=0.001$ and $p=0.032$, respectively). The results were similar if all patients, and not only those with a baseline NLR of ≥2.15, were included in the analysis (Table SII[1]). An additional multivariate logistic regression analysis was performed to specifically address a potential confounding effect of previous biologic treatment. Treatment with TNF-α antagonists remained a significant predictor of a median NLR of <2.15 under treatment if previous treatment with biologics was introduced as a covariate (odds ratio (95% CI): 4.35 (1.0–18.6) and 1.26 (0.5–3.1), $p=0.047$ and 0.615, respectively).

Characteristics of the patients under TNF-α and IL12/23 antagonist treatment are detailed in Table SIII[1]. Treatment duration (mean ± 95% CI 21 ± 3 and 19 ± 5 months, $n=173$ and 23, respectively, $p=0.595$, Student's t-test) and the baseline NLR (2.89 (2.6, 3.2) and 3.07 (2.4, 4.0), $n=148$ and 21, respectively, $p=0.670$, Student's t-test) were not significantly different. While the frequency of co-treatment with methotrexate differed between the groups, its predictive effect on the likelihood of reaching a median NLR below 2.15 under treatment was much smaller than that of biologic class, and missed significance by a considerable margin in the multivariate analyses (Table II, Table SII[1]).

DISCUSSION

First, these results supplement previous publications indicating a rapid reduction in NLR in patients with psoriasis within the first 3 months of biologic treatment (15, 19). Since the follow-up in earlier studies was limited to 12 months, the current data considerably expand the available evidence, by demonstrating that NLR remained stable at a low level under biologic treatment for at least 33 months.

Secondly, to the best of our knowledge, this is the first detailed comparison of NLR dynamics between patients treated with TNF-α and IL-12/23 antagonists. Patients treated with TNF-α antagonists showed a significantly more pronounced decrease in NLR compared with those treated with ustekinumab. A stepwise, multivariate binary regression analysis was used to control for confounding factors and confirmed TNF-α antagonist treatment as an independent predictor of a median NLR below 2.15 over the entire treatment period. The results of the current study are generally in agreement with previous studies by Karabay et al. (16) and Asahina et al. (15) in Turkish and Japanese patients with psoriasis, where NLR decreased more under TNF-α antagonist than under ustekinumab

Table II. Comparison of patients' characteristics based on the median neutrophil-to-lymphocyte ratio (NLR) under treatment

			Multivariate binary logistic regression			
	NLR under treatment		Initial model		Final model	
	≥2.15	<2.15	Exp (B) (95% CI)	Significance	Exp (B) (95% CI)	Significance
Treatments*, *n* (%)	68 (60)	46 (40)				
Age, years, mean±SD	48.3±12	47.5±13	1.00 (1.0–1.0)	0.879		
Sex, female, %	38	37	0.86 (0.3–2.2)	0.754		
Psoriasis arthritis, present, %	50	41	0.46 (0.2–1.3)	0.143		
Previous systemic treatments, mean±SD	3.0±2	2.7±1	0.91 (0.6–1.3)	0.608		
Median [IQR]	3.0 [2, 4]	2.0 [2, 3]				
Biologic, %						
Tumour necrosis factor-α antagonist	79	93	3.83 (0.6–23.8)	0.149	4.68 (1.1–19.1)	0.032
Ustekinumab	21	7				
Concomitant methotrexate, %	12	15	1.60 (0.4–6.3)	0.502		
Treatment duration, years, mean±SD	1.3±1	1.5±1	1.52 (1.0–2.3)	0.050	1.38 (0.9–2.0)	0.100
Baseline PASI, mean±SD, (*n*)	11.2±7 (64)	10.3±7 (42)	0.99 (0.9–1.1)	0.685		
Median [IQR]	9.6 [7, 15]	9.2 [5,14]				
Baseline NLR, mean[SD], (*n*)	4.6 [3, 8] (68)	3.0 [2, 4] (46)	0.55 (0.4–0.8)	0.002	0.53 (0.4–0.8)	0.001
Median [IQR]	4.1 [3, 6]	2.7 [2, 4]				

*Only patients with a baseline NLR ≥2.15 were included in this analysis.
Gmean: geometric mean; IQR: interquartile range; PASI: Psoriasis Area and Severity Index; SD: standard deviation.

treatment. However, these earlier studies were limited to 12 weeks and 12 months, respectively, and no direct statistical comparison between TNF-α antagonists and ustekinumab was performed. The current findings are also in line with previous reports of a more sustained reduction in CRP under TNF-α antagonist compared with ustekinumab treatment in Japanese patients with psoriasis (8). On a cellular level, TNF-α and IL-17 antagonists were shown to suppress leucocyte-endothelium interactions and thrombus formation in patients with psoriasis to a level comparable to that of healthy donors, while leucocytes from patients treated with IL12/23 antagonists continued to display a pro-inflammatory phenotype even in clinical remission (9). IL-17 is thought to provide a link between psoriasis and cardiovascular disease (20). Interestingly, response to etanercept treatment depended on a downregulation of IL-17 pathways to baseline levels (21). On the other hand, beneficial effects of ustekinumab are mainly attributed to blocking of IL-23, while IL-12 may initiate protective effects on IL-17-mediated inflammation, and its collateral targeting may be counterproductive in psoriasis (22). However, the perivascular fat attenuation index (FAI), a marker of coronary inflammation and coronary plaque-burden, was similar between patients treated with either biologic after 1 year (23, 24). At the clinical level, convincing evidence links treatment with TNF-α antagonists to a reduced cardiovascular risk (7, 25–27), while the data for ustekinumab is more complex. On the one hand, the development of the IL-12/23 antagonist briakinumab was halted, in part due to the occurrence of major cardiovascular events (28), ustekinumab was reported to lead to early severe cardiovascular events in patients with high cardiovascular risk (29), and an earlier registry study found worse cardiovascular outcomes in patients treated with IL-12/23 vs TNF-α antagonists over a mean 2 years follow-up (10). On the other hand, an observational study, meta-analysis of randomized controlled trials, and registry study failed to detect differences in cardiovascular risk between the biologics (30–32). However, protective effects on cardiovascular events may take longer to manifest than the limited follow-up of 10–30 weeks (31), 1.5 years (32), and 2 years (30).

The strengths of the present study are its "real-world" setting, long follow-up, and high temporal resolution. The main limitation is its retrospective design. Thus, as is inherent to this design, confounding factors cannot be completely controlled. NLR may be confounded by previous treatments, infections and autoimmune co-morbidities. However, no autoimmune co-morbidities were noted by the treating physicians at baseline. It is not likely that biologic treatment would have been initiated with overt clinical infection at baseline and, based on the known profiles of adverse events, it is not likely that patients under treatment with IL-12/23 antagonists experienced more infectious complications than patients treated with TNF-α antagonist (33). The number of previous systemic treatments and methotrexate co-treatment differed between patients treated with TNF-α and IL-12/23 antagonists (Table SIII[1]). However, the time between cessation of any previous systemic treatment and initiation of the treatment cycle under investigation was 5–6 months (168 ± 381 days). The time between cessation of a previous biologic and initiation of the treatment cycle under investigation was 10 months (297 ± 380 days; all mean ± standard deviation (SD)). Thus, as expected, the baseline NLR and PASI were similar between patients treated with TNF-α and IL-12/23 antagonists (2.9 vs 3.1 and 10.3 vs 10.6, respectively, Table SIII[1]). Importantly, previous systemic treatments, which include previous biologic treatments and may point towards a more recalcitrant disease, and methotrexate co-treatment were included in a multivariate logistic regression analysis and, in contrast to TNF-α antagonist treatment, did not significantly affect the likelihood of reaching a median NLR of < 2.15 under treatment (Table SII[1]). Furthermore, the significant positive predictive effect of TNF-α antagonist treatment on a median NLR of less than 2.15 was independent of previous biologic treatment (cf. Results). Finally, the median PASI under treatment was not significantly different between patients treated with TNF-α and those treated with IL-12/23 antagonists (2.9 vs 3.0, cf. Results) indicating that, regarding cutaneous response, patients from both groups performed similarly. As a further possible limitation, cardiovascular endpoints were not directly investigated, but NLR was used as a proxy for systemic disease. This approach is, however, supported by a variety of studies, notably concerning systemic inflammation in the field of cardiovascular medicine, indicating that biomarkers are well-suited to identify at-risk populations (34, 35). Furthermore, as mentioned above, biomarkers are helpful surrogate criteria, as protective effects on cardiovascular events may take a very long time to manifest. The current study focused on 2 older classes of biologics, which have been available for a long time. However, they are still considered among the first- and second-line options for patients with cardiovascular co-morbidity (36). Nonetheless, research to re-examine the current findings in newer generation biologics would be desirable.

In conclusion, this study found a rapid and stable reduction in NLR, a biomarker of systemic inflammation and independent risk factor for cardiovascular disease, under biologic treatment. The reduction was significantly more pronounced, and the likelihood of reaching low cardiovascular risk NLR levels was significantly and considerably higher under TNF-α compared with IL-12/23 antagonist treatment. These findings expand considerably on previous data and suggest class-specific effects of biologics on systemic inflammation, which could be relevant for the prevention of psoriasis co-morbidity by biologic treatment. Further clinical trials assessing differential effects of biologics on systemic inflammation and long-term studies assessing cardiovascular endpoints are necessary.

The authors have no conflicts of interest to declare.

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