

CLINICAL REPORT

Survival and Effectiveness of Tumour Necrosis Factor- α Inhibitors in the Treatment of Plaque Psoriasis under Daily Life Conditions: Report from the Psoriasis Registry Austria

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This retrospective multicentre analysis from the Psoriasis Registry Austria (PsoRA) was conducted to determine drug effectiveness and survival of anti-tumour necrosis factor alpha (anti-TNF- α) agents in patients with moderate-to-severe chronic plaque psoriasis over a 9-year period. Data on 1,019 treatment cycles with adalimumab ($n=460$), etanercept ($n=501$), and/or infliximab ($n=58$) administered to 827 patients (272 women, 555 men) were available for analysis. Compared with etanercept, adalimumab and infliximab showed superior short-term effectiveness. Intention-to-treat-calculated median drug survivals for adalimumab (1,264 days) and etanercept (1,438 days) were similar to each other ($p=0.74$), but significantly superior to that of infliximab (477 days) ($p=7.0e-07$ vs. adalimumab and $p=2.2e-07$ vs. etanercept, respectively). Their drug survival rates at 36 months were 51.6%, 56.0%, and 22.6%, respectively. Survival rates correlated significantly with effectiveness for adalimumab and etanercept, but not for infliximab. **Key words: psoriasis; biologics; drug survival; effectiveness; daily life conditions.**

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Treatment of psoriasis with biologic agents has been shown to be clinically efficacious and well tolerated in

numerous randomized clinical trials (RCT) (1). However, the results of RCTs are not thought to be directly generalizable to patients outside of such studies (2, 3). In daily clinical practice, drug survival, and ultimately patient outcomes, may be influenced by a combination of factors, including drug effectiveness, treatment or patient satisfaction, availability of other treatment options, and occurrence of severe or disturbing side-effects (2, 4, 5). The present study retrospectively analysed survival and long-term effectiveness of the anti-TNF- α agents adalimumab, etanercept, and infliximab in patients with moderate-to-severe chronic plaque psoriasis treated in daily clinical practice in Austria.

METHODS

Study design

This was an observational retrospective multicentre study of clinical data extracted from the Psoriasis Registry Austria (PsoRA; <http://www.psoriasisregistry.at>). This web-based nationwide registry contains data from patients with psoriasis being treated under daily life conditions outside of clinical trials, in university dermatology departments, non-university dermatology departments, and private dermatology practices. In particular, PsoRA collects demographic data, data on drug survival and adverse events of systemic psoriasis treatments, phototherapy, and selected topical treatments from patients with moderate-to-severe psoriasis. The registry also contains data on Psoriasis Area and Severity Index (PASI) scores and specific PASI reduction categories (i.e. complete remission (CR) and PASI reduction by 90% (PASI 90), 75% (PASI 75), 50% (PASI 50) and <50% (PASI <50)). The registry was approved by the ethics committee of the Medical University of Graz (application number 21-094 ex 09/10), and this study was conducted in accordance with the principles of the Declaration of Helsinki.

Study setting

The present study analysed data from adult patients whose moderate-to-severe chronic plaque psoriasis was treated regularly with the anti-TNF- α agents adalimumab, etanercept and/or infliximab between October 2004 and September 2013. Data were collected in 16 centres in Austria, including 4 university dermatology departments, 10 non-university dermatology departments and 2 private dermatology practices.

Study population

Of 1,431 patients registered in the PsoRA database, 827 met the criteria for this analysis (i.e. ≥ 18 years of age with chronic plaque psoriasis that had been treated with at least one course of adalimumab, etanercept and/or infliximab). The prerequisites for allocation to a biologic and its treatment cost reimbursement in Austria have been described previously (4). The present analysis excluded treatment cycles in which concomitant systemic therapy and/or phototherapy was given from the start of those cycles to the time scheduled for the assessment of first definite response (i.e. 4 months). If concomitant systemic therapies were given as rescue to augment effectiveness after 4 months, these cycles were considered in the intention-to-treat (ITT), per-protocol (PP) and worst-case scenario (WC) analyses described below. Almost all patients had a concomitant topical treatment with corticosteroids and/or vitamin D analogues.

Assessment of drug survival and effectiveness

A treatment cycle was defined as an allocation of a biologic agent to a patient, irrespective of the length of that treatment. Drug survival (i.e. time to drug discontinuation) for a patient was calculated as the total duration, in days, for which the patient was on treatment after its start until discontinuation. In the survival analysis there was no minimum time for treatment. Median drug survival was defined as the time at which 50% of the patients had discontinued treatment. Effectiveness was analysed in terms of PASI reduction score, where 1=CR, 2=90–<100% reduction, 3=75–<90% reduction, 4=50–<75% reduction, and 5=<50% reduction, averaging the resulting values. Effectiveness at a time-point was obtained from the nearest visit data by linear interpolation.

Statistical analysis

Duration of drug survival was analysed by survival analysis, as the end of treatment was not observed for many patients. The reason for censoring has to be statistically independent from drug survival (e.g. because a patient was not on treatment for long enough). Patients without a record of end of treatment at the last visit of the treatment cycle were thus censored; otherwise the end of drug survival was recorded. For patients who started a concomitant therapy during a treatment cycle, the following scenarios were calculated. In ITT analysis concomitant therapy was ignored. In PP analysis cycles were recorded as censored from the start of concomitant therapy in the survival analysis and were considered as missing values from the start of concomitant treatment for effectiveness analysis. In WC analysis the start of concomitant systemic and/or phototherapy therapy was recorded as the end of drug survival. Drug survival was analysed by Kaplan–Meier estimates. Cox regression was performed to identify risk factors for the end of drug survival. R 3.1.2 (www.r-project.org) was used for calculations. The cluster option of the package survival 2.38-1 of R was applied to properly analyse patients with multiple treatments with anti-TNF- α agents. The independence working model, as implemented in package gee 4.13-18 of R, was applied for the

same purpose in analysis of variance. Analysis of variance was used to compare effectiveness data. If the end of treatment was observed, the length of drug survival and mean PASI reduction score were correlated using Spearman's correlation coefficient. All statistical tests were 2-sided at the 0.05 significance level.

RESULTS

Patients and treatment characteristics

Data from a total of 827 patients (272 women, 555 men) who were administered a total of 1,026 anti-TNF- α treatment cycles over 2,572 patient-years of follow-up were analysed retrospectively. At first treatment cycle, the median age and disease duration were 46 years (range 18–80 years) and 18 years (range 0–56 years), respectively. Seven cycles were excluded from the analysis because of missing data. Of the remaining 1,019 treatment cycles, 460 cycles used adalimumab, 501 used etanercept, and 58 used infliximab (Table I). The median PASI at treatment start was 13.9 (4.2–47.2), 14.0 (0–43.1) and 17 (7.4–45.9) in treatment cycles with adalimumab, etanercept and infliximab, respectively (Table I). A total of 171 patients received 2 or more biologic treatments. The most frequent treatment switch between anti-TNF- α agents was from etanercept to adalimumab (87 cycles) (Table SI¹). In cases in which an agent was interrupted for at least 3 months, restarting with that agent was considered as a new treatment cycle. This happened in a limited number of cases. Concomitant systemic therapy and/or phototherapy were given as rescue to augment the effectiveness of adalimumab, etanercept and infliximab during 32, 42 and 8 treatment cycles, respectively. The most frequently used concomitant therapy was methotrexate (56 cycles) (Tables I and SIII¹).

Anti-TNF- α drug survival

Upon ITT analysis, the median drug survival was 1,264 days (95% confidence interval (95% CI), 800

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Table I. Characteristics of treatment cycles with anti-tumour necrosis factor- α agents

	Adalimumab	Etanercept	Infliximab
Treatment cycles, <i>n</i>	460	501	58
PASI at treatment start, median (range)	13.9 (4.2–47.2)	14.0 (0–43.1)	17 (7.4–45.9)
Disease duration at treatment start, years, median (range)	16 (1–56)	19 (0–50)	16 (1–37)
Concomitant treatment ^a , <i>n</i> (%)	32 (7.0)	42 (8.4)	8 (13.8)

^aSystemic therapy and/or phototherapy. PASI: Psoriasis Area and Severity Index.

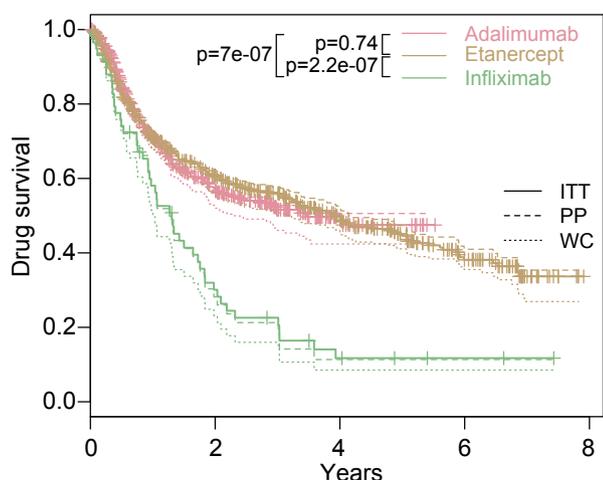


Fig. 1. Drug survival rates for adalimumab, etanercept and infliximab. ITT: intention-to-treat; PP: per-protocol; WC: worst-case scenario analysis, as described in Materials and Methods. *p*-values are shown for ITT analysis.

days to infinity) for adalimumab, 1,438 days (95% CI, 1,141–1,825 days) for etanercept, and 477 days (95% CI, 337–642 days) for infliximab (Fig. 1, Table II). Drug survival rates for adalimumab, etanercept, and infliximab were 70.9%, 70.8% and 58.0%, respectively, at 12 months, 57.0%, 60.8% and 30.1%, respectively, at 24 months, 51.6%, 56.0% and 22.6%, respectively, at 36 months, and 47.5%, 44.6% and 11.7%, respectively, at 60 months. Total relative drug survival in the ITT, PP and WC analyses was similar at all available time-points (Tables II and SIII¹). In the ITT analysis, drug survival durations for adalimumab and etanercept were similar to each other ($p=0.74$), but statistically significantly superior to that of infliximab ($p=7.0e-07$ and $p=2.2e-07$, respectively). Similar results were obtained in the PP and WC analyses (Fig. 1 and Table II).

Table II. Analysis of drug survival and Cox regression analysis of effect of factors on drug survival

	Intention-to-treat	Per-protocol	Worst-case
Median drug survival ^a , days (lower–upper 95% CI)			
Adalimumab	1,264 (800–infinity ^e)	– ^b (876–infinity ^e)	840 (680–1,264)
Etanercept	1,438 (1,141–1,825)	1,512 (1,253–1,982)	1,162 (785–1,466)
Infliximab	477 (337–642)	463 (338–642)	366 (272–484)
Hazard ratio and <i>p</i> -value for comparison of median drug survival			
Adalimumab vs. etanercept	0.97 ($p=0.74$)	0.96 ($p=0.68$)	0.94 ($p=0.56$)
Adalimumab vs. infliximab	2.10 ($p=7.0e-07$)	2.20 ($p=5.5e-07$)	2.20 ($p=6.7e-08$)
Etanercept vs. infliximab	2.20 ($p=2.2e-07$)	2.20 ($p=2.2e-07$)	2.20 ($p=2.2e-07$)
Hazard ratio and <i>p</i> -value for different factors			
Age (per 10 years)	0.92 ($p=0.030$) ^c	0.92 ($p=0.033$) ^c	0.94 ($p=0.100$)
Male sex	0.78 ($p=0.013$)	0.75 ($p=0.006$)	0.75 ($p=0.003$)
Disease duration (per 10 years)	0.87 ($p=0.024$) ^d	0.87 ($p=0.023$) ^d	0.89 ($p=0.050$) ^d

^aMedian drug survival was defined as the time at which 50% of the patients had discontinued treatment. ^bTime not reached at which 50% of the patients had discontinued treatment. ^cThe older the patient, the significantly longer the drug survival. ^dThe longer the disease duration, the significantly longer the drug survival. ^eInfinity: the upper limit of the confidence interval could not be calculated from the available data (as the survival curves for adalimumab did not reach the 0.5 (50%) value). CI: confidence interval.

In the analysis presented here we excluded treatment cycles in which concomitant systemic therapy and/or phototherapy was given from the start of those cycles. However, we also analysed drug survival using data from all treatment cycles as retrospectively observed, including cycles to which concomitant systemic and/or phototherapy was given from the start of those cycles (adalimumab, $n=511$, including combination with methotrexate, $n=32$; others, $n=19$); etanercept, $n=550$, including combination with methotrexate, $n=31$; others, $n=18$); and infliximab, $n=85$, including combination with methotrexate, $n=25$; others, $n=2$). This analysis revealed similar results for ITT, PP and WC, irrespective of whether those cycles were included (data not shown).

In the ITT analysis, longer drug survival was statistically significantly associated with higher age ($p=0.03$), male sex ($p=0.013$) and longer disease duration ($p=0.024$) (Table II). Similar results were observed in the PP analysis (Table II). In the WC analysis, longer drug survival was statistically significantly associated with male sex and longer disease duration only (Table II). For all analyses, drug survival was not statistically significantly associated with either concomitant disease or previous anti-TNF- α therapy (naïve vs. exposed patients).

During the observation period, treatment was discontinued in 176 of 460 (38.3%) adalimumab cycles, 245 of 501 (48.9%) etanercept cycles, and 48 of 58 (82.8%) infliximab cycles. Overall, the main reason for discontinuation was loss of initial response in a total of 140 (13.7%) cycles, including 45 (9.8%) adalimumab cycles, 81 (16.2%) etanercept cycles, and 14 (24.1%) infliximab cycles (Table III). Adverse events led to treatment discontinuation in 17 (3.7%) adalimumab cycles, 27 (5.4%) etanercept cycles, and 7 (12.1%) infliximab cycles, respectively (Table III). Overall, the most frequent adverse event leading to treatment discontinuation was infection, in 10 treatment cycles. All reported reasons for treatment discontinuation and adverse events are shown in Tables IV and SIV¹.

Effectiveness

In the ITT analysis, PASI 75 was observed in 264 of 406 (65%) adalimumab cycles, 223 of 449 (49.7%) etanercept cycles, and 37 of 53 (69.8%) infliximab cycles at 4 months. PASI 90 was observed in 145 (35.7%) adalimumab cycles, 95 (21.2%) etanercept cycles, and 27 (50.9%) infliximab cycles at that time-point (Table SVI¹).

As shown by ITT analysis, mean PASI reduction scores achieved

Table III. Reasons for treatment discontinuation

Reason for treatment discontinuation ^a	Treatment cycles, n (%) ^c		
	Adalimumab	Etanercept	Infliximab
Primary ineffectiveness ^b	49 (10.7)	55 (11)	5 (8.6)
Loss of initial response	45 (9.8)	81 (16.2)	14 (24.1)
Adverse event	17 (3.7)	27 (5.4)	7 (12.1)
Patient wish	2 (4.8)	36 (7.2)	7 (12.1)
Switch to another biologic agent	6 (1.3)	12 (2.4)	3 (5.2)
Complete remission ^b	10 (2.2)	11 (2.2)	6 (10.3)
Other reason	27 (5.9)	23 (4.6)	6 (10.3)
Total	176 (38.3)	245 (48.9)	48 (82.8)

^aIncluding all treatment cycles discontinued before or after 4 months of treatment. ^bNon-responder. ^cThe percentages refer to the total number of treatment cycles depicted in Table I.

with adalimumab ($n=406$) were 3.1 at 4 months, 2.8 ($n=363$) at 6 months, 2.4 ($n=259$) at 12 months and 2.3 ($n=25$) at 48 months. Mean PASI reduction scores achieved with etanercept ($n=449$) were 3.4 at 4 months, 3.2 ($n=412$) at 6 months, 2.9 ($n=330$) at 12 months and 2.7 ($n=136$) at 48 months. Mean PASI reduction scores achieved with infliximab ($n=53$) were 3.0 at 4 months, 2.8 ($n=45$) at 6 months, 3.1 ($n=36$) at 12 months and 2.5 ($n=6$) at 48 months (Fig. 2; 48 months data not plotted).

Results of ITT analyses are presented in Table SV¹. Similar results were obtained in PP analysis (data not shown). All effectiveness data (including ITT and PP analysis results), the total number of treatment courses, and the percentages of treatment courses that resulted in CR, PASI 90, PASI 75, and PASI 50 are presented in Tables SV¹ and SVI¹.

Drug survival and effectiveness

Spearman's correlation coefficients for length of drug survival and PASI reduction scores for adalimumab, etanercept and infliximab were -0.29 ($p=0.00018$), -0.16 ($p=0.01$) and -0.14 ($p=0.34$), respectively, indicating a direct correlation of length of drug survival and effectiveness (Table SVII¹).

Table IV. Adverse events that had resulted in treatment discontinuation

Type of adverse event	Treatment cycles, n			
	A	E	I	All agents
Injection site reaction	4	4	0	8
Infection	2	8	0	10
Rash	1	0	0	1
Malignancy	1	0	0	1
Gastrointestinal symptoms	0	2	1	3
Liver toxicity	0	6	0	6
Neurological symptoms	1	2	1	4
Systemic reaction/anaphylaxis	3	1	4	8
Other	2	2	0	4
Not available	3	2	1	6
Total	17	27	7	51

A: Adalimumab; E: Etanercept; I: Infliximab.

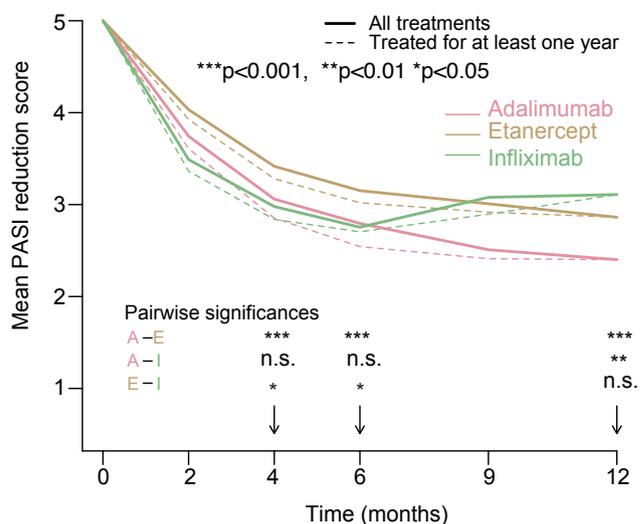


Fig. 2. Intention-to-treat analysis of mean Psoriasis Area and Severity Index (PASI) reduction scores achieved with adalimumab, etanercept and infliximab. All treatments: data from all cycles analysed ($n=707$), irrespective of length of treatment. Treated for at least one year: data only from cycles of patients who had been treated for at least one year ($n=625$). For definition of mean PASI reduction score see methods.

DISCUSSION

In this study drug survival was analysed using 3 different methods (i.e. ITT, PP and WC analysis). This may be a rather elaborate technique; however, we consider this to be one of the most accurate methods of analysing treatments in patients who have also received concomitant medication. These 3 methods of analyses led to similar results, with no significant differences in drug survival among the different types of analyses.

However, several studies have investigated survival for anti-TNF- α agents for the treatment of psoriasis in daily clinical practice, but have also produced controversial results (2, 6–12). For instance, infliximab was found to be inferior (7, 8), equal (10), or superior (6) in drug survival compared with adalimumab and/or etanercept. In the present study, however, drug survival durations for adalimumab and etanercept did not differ significantly from each other ($p=0.74$), but were superior to that of infliximab ($p=7.0e-07$ and $p=2.2e-07$, respectively).

These clear discrepancies between the findings of different daily practice studies (2, 6–11) and our present analysis may be due to several factors. Those factors include differences in patient cohorts, previous treatments (naive vs. not naive to anti-TNF- α agents) (13), potential adjustments in dose or alterations in dose intervals (9, 14), allocation and reimbursement policies, and physician and patient treatment preferences in different countries. However, comparing such studies is difficult. For example, the present analysis excluded treatment cycles in which concomitant systemic therapy and/or phototherapy was given from the start of those

cycles because it has not been a standard procedure in Austria. On the other hand, concomitant treatment with methotrexate (15) is standard for infliximab therapy from the start of treatment in other countries. Consequently, drug survival of infliximab might have been underestimated in some analyses compared with other studies (6). However, we also analysed drug survival using data from all treatment cycles and found similar results for ITT, PP and WC analyses, irrespective of whether those cycles with concomitant and/or phototherapy were included (data not shown). Moreover, the consecutive introduction of new biologics over the past 10 years and the related route of administration (intravenous vs. subcutaneous, with its potential for higher patient satisfaction) may have contributed to the lower drug survival of infliximab observed in our study. In addition, infliximab was the first biologic agent approved for psoriasis in Austria, although it is now very rarely used as a first-line biologic and its use as a last-resort biologic has declined a great deal over the years.

The present study found that overall longer drug survival was statistically significantly associated with higher age ($p=0.03$), male sex ($p=0.013$), and longer disease duration ($p=0.024$). The association of drug survival with male sex is consistent with observations in other daily practice studies (2, 6, 8), but the association with disease duration and age is not. The main reason for loss of drug survival in our present study was ineffectiveness (i.e. loss of initial response and primary ineffectiveness) (Tables III and SIV¹) in a total of 249 treatment cycles (24.4%). This observation is consistent with the results of previously reported daily practice studies of anti-TNF- α agents for psoriasis (2, 6, 8–10).

At present, one of the most important biologic agents after TNF- α agents is ustekinumab. Thus, we analysed preliminary data for drug survival of ustekinumab from our registry (212 patients with a total of 216 treatment cycles with ustekinumab) (16). At 12, 24 and 36 months (with 118, 47 and 9 ongoing patient treatment cycles, respectively), drug survival of ustekinumab was 89.1%, 80.4% and 75.6%, respectively (16). The observed drug survival rate of ustekinumab was higher than that for adalimumab, etanercept and infliximab, as reported in the current study and documented in PsoRA. This is consistent with recent reports by van den Reek et al. (9) and Gniadecki et al. (12) showing a clear superiority for ustekinumab, surpassing any other anti-TNF- α agent in long-term drug survival.

ITT analysis of long-term effectiveness showed that the mean PASI reduction scores achieved with adalimumab were statistically superior to those achieved with etanercept from 4 to 48 months, but superior to those achieved with infliximab only at 12 and 24 months. In addition, the mean PASI reduction scores achieved with infliximab were statistically superior to those achieved

with etanercept at 4 and 6 months, but not from 12 to 48 months of therapy. However, at later time-points, only a few patients remained on infliximab treatment and the power would probably have been too low to show statistical significance.

Treating psoriasis with anti-TNF- α agents has been shown to be very effective, not only in various multi-centre RCTs (1), but also clinical practice studies (2, 10, 13, 17–24). However, because treatment response rates depend on drug dose (particularly in the induction phase), dosing interval, timing of response evaluation, and statistical analysis type, comparing such studies is difficult. For instance, the few daily practice studies that have been published in the literature show variable PASI response rates to variable treatment doses at variable time-points (2, 10, 13, 17–24). Very recently, Menting et al. (10) reported PASI 75 rates of 53.6%, 31.5% and 53.9% for adalimumab, etanercept and infliximab, respectively, after 3 months of therapy. In the current study PASI 75 rates of 65.0%, 49.7% and 69.8% were observed for adalimumab, etanercept, and infliximab, respectively, after 4 months of therapy.

The relationship of effectiveness and drug survival were analysed in our cohort. This type of analysis, which has rarely been performed in other studies is a major strength of our study, in addition to other factors, such as the relatively large number of patients and long observation period of 9 years. Drug survival correlated significantly with effectiveness for adalimumab and etanercept, but not for infliximab (Table SVII¹). Drug survival for the latter drug may have been driven mainly by loss of initial response, adverse events, patient adherence, switch to other biologic agent, and CR (Table III). Alternatively, as mentioned before, the number of patients on infliximab treatment was not very high and the power may have been too low to show a statistically significant correlation of its drug survival with effectiveness.

Limitations of our study are its retrospective set-up and the fact that PsoRA does not require inclusion of the exact doses and intervals of the biologics administered to patients in the database. This raises the possibility that any differences in the dosing regimens for particular biologic agents (e.g. etanercept administered 50 mg weekly vs. 25 mg twice weekly vs. 50 mg twice weekly) could have contributed to differences in PASI response among the biologics analysed in our present study, particularly at the early time-points.

Conclusion

Median drug survivals for adalimumab and etanercept were similar to each other (i.e. 1,264 days (42 months) vs. 1,438 days (48 months)), but superior to that of infliximab (i.e. 477 days (16 months)). Compared with etanercept, adalimumab and infliximab showed

superior short-term effectiveness, but similar long-term effectiveness, as measured in terms of mean PASI reduction. Differences in survival rates among various studies in the literature may be due to differences in physician and patient preferences and differences in national allocation and reimbursement policies for anti-TNF- α treatments.

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