Received: 10 November 2020 | Accepted: 27 November 2020

DOI: 10.1111/dth.14623

ORIGINAL ARTICLE

DERMATOLOGIC THERAPY WILEY

Retention and survival rate of etanercept in psoriasis over 15 years and patient outcomes during the COVID-19 pandemic: The real-world experience of a single center

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Abstract

There have been a number of investigations of the efficacy and safety of etanercept. This study was performed to obtain long-term drug survival data (ie, time to drug discontinuation) for etanercept, and the reasons for its discontinuation. The study population consisted of patients with psoriatic arthritis and psoriasis followed up by our clinic, registered in the Turkish Psoriasis Registry (PSR-TR) and treated with etanercept for at least 4 weeks between January 1, 2005, and January 31, 2020. The efficacy of etanercept was evaluated in terms of the Psoriasis Area and Severity Index (PASI) 75, PASI 90 and PASI 100 response rates at 12, 24, 36, and 48 weeks, and annually thereafter. The behaviors of the patients with respect to the use of etanercept, and the outcomes of those who continued to use it during the COVID-19 pandemic, were also investigated.

KEYWORDS

anti-TNF treatment, COVID-19, etanercept, psoriasis, retention rate

1 | INTRODUCTION

Etanercept is a tumor necrosis factor (TNF) antagonist approved for the treatment of psoriatic arthritis and psoriasis. The anti-inflammatory effects of etanercept are due to its ability to bind the proinflammatory cytokine, TNF, preventing it from interacting with cell-surface receptors.

Etanercept has shown efficacy in a high percentage of patients. Several trials have reported the safety and efficacy of etanercept.[1-7] The present study was performed to determine the long-term efficacy and safety of etanercept, the demographic characteristics of patients, and drug survival (ie, time to drug discontinuation) over a period of 15 years.

2 | PATIENTS AND METHODS

This was an observational retrospective study including 247 patients with moderate to severe plaque psoriasis who received etanercept at a dose of 50 mg/week for at least 4 weeks. Approval for the study was obtained from the local Ethics Committee of Bezmialem Vakif University. Patients followed up by our clinic and registered in the Turkish Psoriasis Registry (PSR-TR) treated with etanercept (50 or 100 mg) weekly for at least 4 weeks between January 1, 2005, and January 31, 2020, were included. The data obtained from the PSR-TR were checked against the hospital records. Baseline demographic data, including age, sex, body mass index (BMI), presence of arthritis, date of etanercept initiation, duration of use, and date of and reasons for discontinuation were obtained from the registry. History of SARS-CoV2 infection, and behavior during the pandemic (ie, continuing or stopping treatment) and outcomes, were investigated.

The severity of psoriasis was determined using the Psoriasis Area and Severity Index (PASI) at baseline, and at 12, 24, 36, and 48 weeks and then at 1, 3, 5, and 10 years. Treatment efficacy was indexed by the PASI 75, PASI 90 and PASI 100 response rates. Dose increases, additional treatments and outcomes thereof, and mild and serious side effects were recorded. Reasons for drug continuation and discontinuation were also determined.

2.1 | Statistics

The distribution of the data was examined using the Shapiro-Wilk test. Descriptive statistics are given as the mean ± SD (SD), median (range) and *n* (%). Backward linear regression analysis was performed to determine the factors affecting the duration of etanercept treatment. Comparisons of categorical variables were performed using Fisher's exact test and the Fisher-Freeman-Halton test. The log-rank test was used to determine differences between Kaplan-Meier survival curves. Mean survival times were determined. All analyses were performed using IBM SPSS Statistics for Windows ([version]; IBM Corp., Armonk, New York). In all analyses, $P < .05$ was taken to indicate statistical significance.

3 | RESULTS

We identified a total of 247 patients with plaque psoriasis, with or without joint involvement, treated with etanercept for at least 4 weeks between January 1, 2005, and January 31, 2020. The patients, 114 (46.2%) women and 133 (53.8%) men, had a mean age of 48.16 ± 14.6 years. Eight children who were resistant to conventional treatments were also included. There was a family history of psoriasis in 95 (38.6%) cases and 130 (52.6%) of the patients had psoriatic arthritis. The mean BMI was 28.71 ± 6.18. The data for BMI and other patient characteristics are shown in Table 1.

TABLE 1 Patient characteristics

	n = 247
Sex	
- Female	114 (46.2%)
- Male	133 (53.8%)
Age (years), mean ± SD (range)	48.16 ± 14.6 (14-88)
Age at onset of disease (years), mean ± SD (range)	25.41 ± 14.7 (0-90)
Weight (kg), mean ± SD (range)	79.41 ± 18.65 (18-170)
Height (cm), mean ± SD (range)	165.44 ± 12.01 (68-192)
BMI (kg/m^2), mean ± SD (range)	28.71 ± 6.18 (15-48.7)
- Normal (BMI < 25), n (%)	64 (25.91%)
- Overweight (BMI 25-29.99), n (%)	84 (34.01%)
- Obese (BMI 30-40), n (%)	79 (31.98%)
- Morbidly obese (BMI > 40), n (%)	13 (5.26%)
Family history of psoriasis, n (%)	95 (38.6%)
Presence of psoriatic arthritis, n (%)	130 (52.6%)

Abbreviation: BMI, body mass index.

3.1 | Duration of treatment

The mean duration of treatment was 28.39 ± 28.65 months (range: 1-156 months), and the median and maximum duration of treatment was 17 months and 13 years, respectively. Thirty-six patients (14.5%) were lost to follow-up. At the time of study completion, 64 patients were continuing to receive etanercept and 33 patients started treatment in the last 5 years of the study period (ie, 2015-2020). While 84 patients (34%) received intermittent therapy, the remaining patients received continuous treatment. Methotrexate or acitretin was added to etanercept in 77 patients (31.1%) because of an inadequate treatment response. As the dose of 50 mg/week was not sufficient in 34 (13.7%) patients, it was increased to 100 mg/week (Table 2). Most of these patients were obese. The PASI 75 response rate was achieved in 51.6% (*n* = 99) of the patients at 12 weeks, and in 65.8% (*n* = 96) at 24 weeks. The PASI 75 response was maintained for 1 year in 68.9% (*n* = 62) of the patients (Figure 1). In the third year, 46.4% (*n* = 26) of the patients achieved PASI 75, 23.2% (*n* = 13) achieved PASI 90 and 12.5% (*n* = 7) achieved PASI 100. In the fifth year, 66.7% (*n* = 18) of the patients achieved PASI 75, 33.3% (*n* = 9) achieved PASI 90 and 14.8% (*n* = 4) achieved PASI 100 (Figure 2).

Etanercept treatment was continued for less than 5 years in 87% (*n* = 215) of the patients. While 11% (*n* = 27) of the patients continued etanercept treatment for a period of 5-10 years, only 2% (*n* = 5) continued the treatment for more than 10 years.

Reasons for discontinuation were ineffectiveness (n = 101 patients; 41%), patient's choice (n = 55; 22%) and pregnancy planning (n = 4; 1.6%). Twenty-six (10.5%) patients discontinued treatment because of adverse effects. The most common side effect was an increase in liver enzyme levels (n = 17; 6.9%). However, as these patients received additional isoniazid (isonicotinic acid hydrazide, INH) for prophylaxis against tuberculosis, this effect may not have been directly attributable to etanercept. During this period, two patients developed pulmonary tuberculosis (reactivation of latent tuberculosis) despite INH prophylaxis. Other serious adverse events occurring during etanercept treatment were renal cell cancer in one male patient and autoimmune nephritis in one female patient (Table 2). No other serious adverse events occurred.

With approval from the Ministry of Health, etanercept treatment was started in eight children who were resistant to phototherapy and conventional therapies. The children consisted of three (37.5%) girls and five (62.5%) boys with a mean age of 13.2 ± 2.586 years (range: 10-17 years). The mean duration of treatment was 46.1 months (median, 36 months) and treatment was terminated in two of these patients because of side effects (urticarial reaction and polymenorrhea), and in one patient because of "secondary ineffectiveness". Treatment was continued in the remaining five pediatric patients. Retention of etanercept and other characteristics of the pediatric patients are shown in Table 3, and PASI response rates at each time point are shown in Figure 3.

In the linear regression analysis, sex, etanercept treatment line, and use in combination with methotrexate/acitretin and/or a dose increase, significantly affected the duration of etanercept usage. Use

TABLE 2 Drug survival and reasons for discontination

	n = 247
Duration of treatment (months), mean (±std), median, (range)	28.39 (±28.65), 17 (1-156)
Continuation of treatment	64 (25.91%)
Patients who have used etanercept;	
Less than 5 years	215 (87%)
Between 5 to 10 years	27 (11%)
More than 10 years	5 (2%)
Patients received etanercept intermittently, n (%)	84 (34%)
Presence of switch to another biological agent	101 (40.9%)
Switch causes	n = 100 (1 missing)
Primer ineffectiveness	35 (35%)
Secondary ineffectiveness	59 (59%)
Side effect	1 (1%)
Patient request	2 (2%)
Patient incompatibility	3 (3%)
Cause of discontinuation of treatment other than switch	
Patient's own decision	55 (22%)
Remission	7 (2.8)
Pregnancy or child desire	4 (1.6%)
Side effect	26 (10.5%)
End of drug/appointment delay	7 (2.8%)
Accident/operation	8 (3.2%)
Unfollow	35 (14.1%)
Treatment modification	n = 94 (38.1%)
Methotrexate	35 (37.2%)
Acitretin	25 (26.6%)
Methotrexate and dose increase	10 (10.6%)
Acitretin and dose increase	7 (7.4%)
Just doze increase	17 (18.1%)
Side effect that require a break or need to be monitored	
Increase in liver enzymes	17 (6.9%)
Tuberculosis	2 (0.8%)
Other infections/malignancy	4 (1.6)
Drug reaction (urticaria, etc.)	6 (2.4%)
Drug side reaction	1 (0.4%)
Proteinuria	1 (0.45)
Other (bleeding, pancytopenia, etc.)	5 (2%)

of etanercept as the first-line biologic agent (biologic-naive patients), use in combination with methotrexate/acitretin and/or a dose increase (treatment modification), and male sex significantly increased the total use of etanercept (Table 4). As shown in Kaplan-Meier curve 1 (Figure 4), the mean total duration of etanercept use was 92.24 ± 8.20 and 58.09 ± 4.83 months in patients with and without treatment modulation, respectively ($P < .001$). As shown in Kaplan-Meier curve 2 (Figure 5), the mean total duration of etanercept use was 86.52 ± 6.68 and 55.05 ± 5.09 months in patients with and without psoriatic arthritis, respectively ($P < .001$).

3.2 | COVID-19 pandemic and behavior of patients

At the time of study completion, 64 patients were continuing to receive etanercept. We contacted 57 of these 64 patients by telephone and confirmed that 41 (72%) continued to use etanercept regularly, without no break during the COVID-19 pandemic. The remaining 16 patients terminated treatment (28%) for the following reasons: 6 patients stopped treatment due to continuation of active work in crowded environments, 5 had concerns regarding safety, 4 could not gain access to the drug, and 1 had to stop because of a cardiovascular operation during this period.

Only one patient had SARS-CoV2 infection confirmed by PCR. This patient was treated at home and stopped etanercept treatment for 1 month.

4 | DISCUSSION

The development of TNF inhibitors represented a breakthrough in psoriasis treatment, but the long-term effects of therapy are still not satisfactory.

This is the first report describing drug survival of etanercept for more than 10 years in Turkey, and the outcomes of patients treated with etanercept during the COVID-19 pandemic. Etanercept is the first TNF inhibitor approved for the treatment of psoriasis in Turkey. There have been large numbers of studies regarding the drug survival rates of various biologics, including etanercept.[1] A retrospective 4-year study in the USA showed that the drug survival rates of biologics were significantly longer than those of conventional therapies.[2] Gniadecki et al suggested that etanercept has a shorter drug survival rate than adalimumab, infliximab and ustekinumab.[8,9] Also, Arnold reported that etanercept tended to show lower survival than other conventional drugs.[10] However, Menting et al found no significant difference in survival rate among biologics.[11]

We did not compare the survival rate of etanercept with those of conventional drugs or other biologics; instead, we specifically investigated etanercept to provide insight that could inform treatment modification, such as dose escalation or use in combination with traditional drugs.

Treatment efficacy was measured based on the PASI response rate, and the rates of PASI 75 were 51.6% ($n = 99$) and 65.8% ($n = 96$) at 12 and 24 weeks, respectively. Van Lümig et al described the long-term efficacy of etanercept in real-world practice; although their response rates were lower than those in randomized controlled trials, the percentage of patients achieving PASI 75 increased progressively from week 12 (23.6%) to week 24 (38.1%).[12,13] In the present study, although the percentage of patients achieving PASI 75 increased

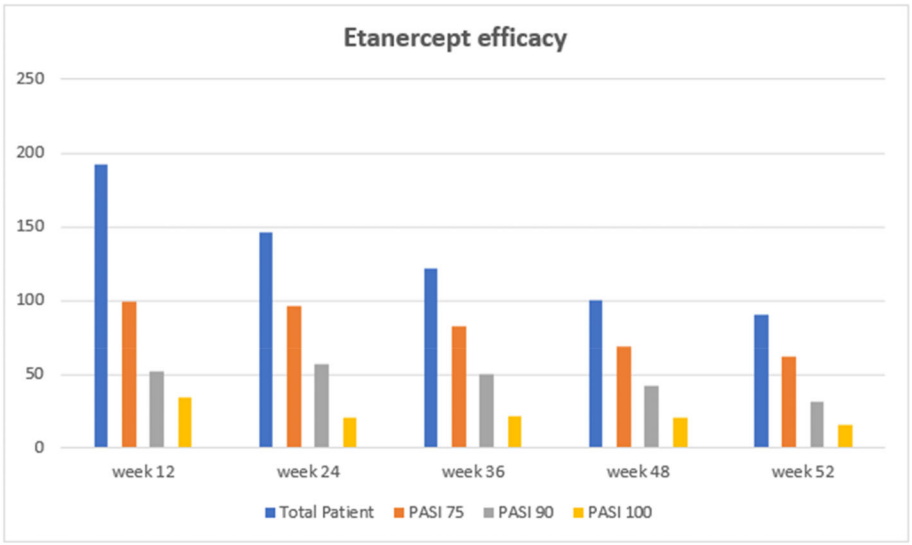


FIGURE 1 Short-term efficacy of etanercept. PASI, Psoriasis Area and Severity Index

Table	week 12	week 24	week 36	week 48	week 52	P Value
PASI 75	51,6%	65,8%	67,2%	69,0%	68,9%	
PASI 90	27,1%	39,0%	41,0%	42,0%	34,4%	p<0.001
PASI 100	17,7%	14,4%	18,0%	21,0%	17,8%	p<0.001
Total Patient	192	146	122	100	90	p<0.001

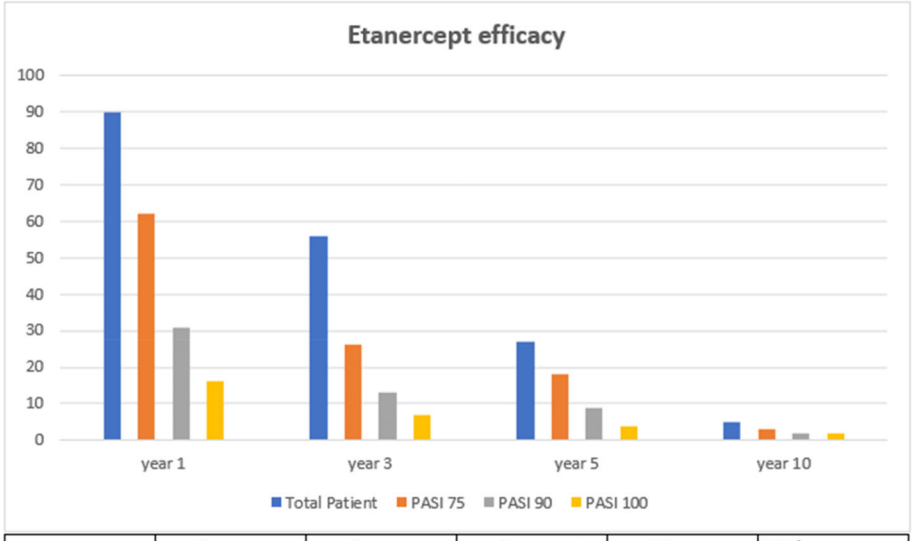


FIGURE 2 Long-term efficacy of etanercept. PASI, Psoriasis Area and Severity Index

	year 1	year 3	year 5	year 10	P Value
PASI 75	68,9%	46,4%	66,7%	60,0%	
PASI 90	34,4%	23,2%	33,3%	40,0%	p<0.001
PASI 100	17,8%	12,5%	14,8%	40,0%	p<0.001
Total Patient	90	56	27	5	p<0.001

progressively in the first 2 years, the response rate began to decrease after 2 years (Figure 2). Etanercept treatment was continued for less than 5 years in the majority of the patients (87%, *n* = 215) because of loss of efficacy, among other reasons. The mean duration of treatment was 28.39 ± 28.65 (range: 1-156) months (Table 2).

The drug survival rate at 13 years in the present study was 2%. Only five patients continued to receive etanercept for >10 years (PASI 100, n = 2; PASI 75, (n = 3). We cannot compare our results with those of other studies because, to our knowledge, no studies have reported a drug survival rate as long as 13 years.

The median duration of etanercept treatment was 36 months in children, which was about double that in adults. The adverse effects were different between the pediatric and adult groups.

Polymenorrhea was observed in an adolescent girl in our series, and was also reported in post-marketing data from the UK.[14]

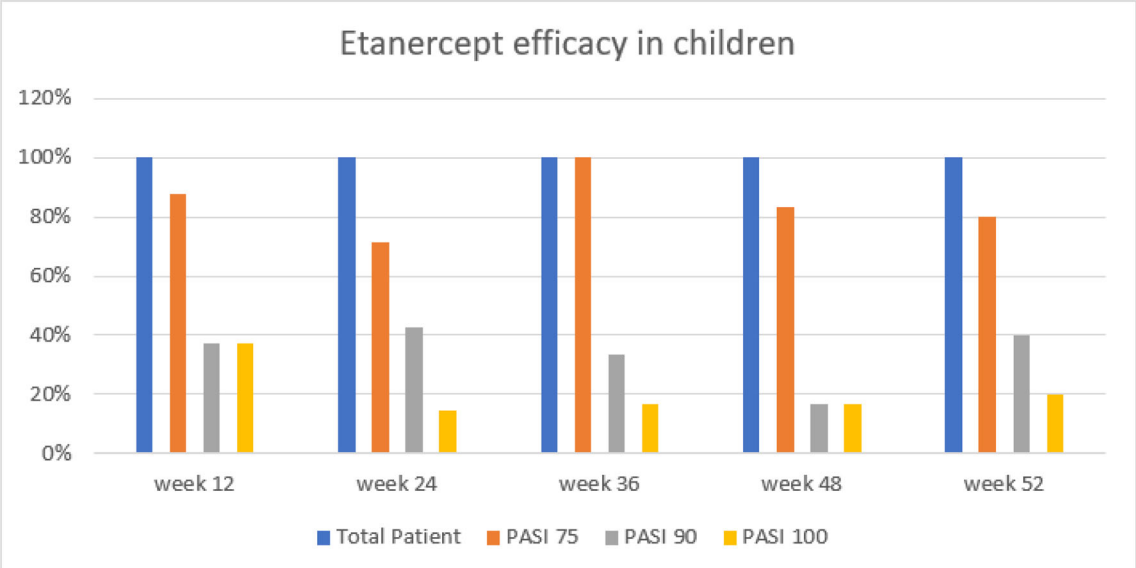
The overall etanercept survival rates were 63%, 41%, 28%, 26%, 13%, 12%, 7%, 2%, and 2% after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 13 years, respectively (Figure 6). Our survival rates were lower than those of previous randomized clinical trials. In a multicenter observational study, Esposito et al reported that etanercept had longer survival than adalimumab and infliximab.[15] We could not make such a comparison because this was not a comparative study.

TABLE 3 Pediatric patient characteristics

	n = 8
Sex	
- Female	3 (37.5%)
- Male	5 (62.5%)
Age (years), mean ± SD (range)	13.25 ± 2.586 (10-17)
Age at onset of disease (years), mean ± SD (range)	8.5 ± 4.2 (1-17)
Weight (kg), mean ± SD (range)	51.25 ± 15.95 (28-75)
Height (cm), mean ± SD (range)	153 ± 17.99 (121-183)
BMI (kg/m^2), mean ± SD (range)	21.31 ± 2.87 (17.6-26.23)
Presence of family history of psoriasis, n (%)	0 (0%)
Presence of psoriatic arthritis, n (%)	2 (25%)
Duration of treatment (months), mean ± SD, median (range)	46.1 ± 33.3, 36 (5-88)
Retention rate after 5 years, n (%)	5 (62%)
Mean PASI on initiation of treatment, mean ± SD, median (range)	9.45 ± 6.51 (1.6-20)

Abbreviations: BMI, body mass index; PASI, Psoriasis Area and Severity Index.

Drug survival time reflects patient adherence to treatment. PASI 90 and 100 are the desired response rates, but such success may be achieved for a short period, before declining over time; even the more realistic PASI 75 response declines over time. Adherence of patients was high within the first 2 years in this study, but declined over time due to lack of efficacy, side effects and patient dissatisfaction. The median duration of etanercept treatment was 17 months, similar to the results of Esposito et al.[15] Children showed a longer median duration of etanercept treatment (36 months), and a retention rate of 62% after 5 years. However, Khraishi et al also reported that retention was longer in their young patient group (<18 years old), but the difference was not statistically significant compared to patients older than 18 years.[16] As the number of pediatric patients in our study was small, our results were not statistically significant. In the present study, retention time was better in male than female patients. Khraishi et al reported no difference in retention rate between female and male patients.[16] In the present study, adherence was higher in male than female patients, and male sex was a positive predictor of adherence. The presence of arthritis and use of etanercept as a first-line biologic agent were also positive predictors of retention rate. Also, Frazier-Mironer et al reported that etanercept had a better retention rate than adalimumab and infliximab as first-line biotherapy.[17] In cases with an insufficient treatment response, we found that adding a



	week 12	week 24	week 36	week 48	week 52
Total Patient	100%	100%	100%	100%	100%
PASI 75	88%	71%	100%	83%	80%
PASI 90	38%	43%	33%	17%	40%
PASI 100	38%	14%	17%	17%	20%

FIGURE 3 Efficacy of etanercept in children. PASI, Psoriasis Area and Severity Index

	β	Std. error	P-value	95% CI
Constant	25 354	8969	.005	7683:43026
Age	0.243	0.125	.053	−0.003:0.489
Sex	10 063	3461	.004	3244:16883
Family history of psoriasis	0.392	3532	.912	−6567:7351
Weight	−0.142	0.097	.146	−0.334:0.050
Use of etanercept as line of treatment	−8251	2840	.004	−13 847:2655
Treatment modulation	12 268	3583	.001	5208:19328

TABLE 4 Linear regression analysis in total use of etanercept

Note: *General significance of the mode $P < .001$ * Adjusted R square = 0.174.

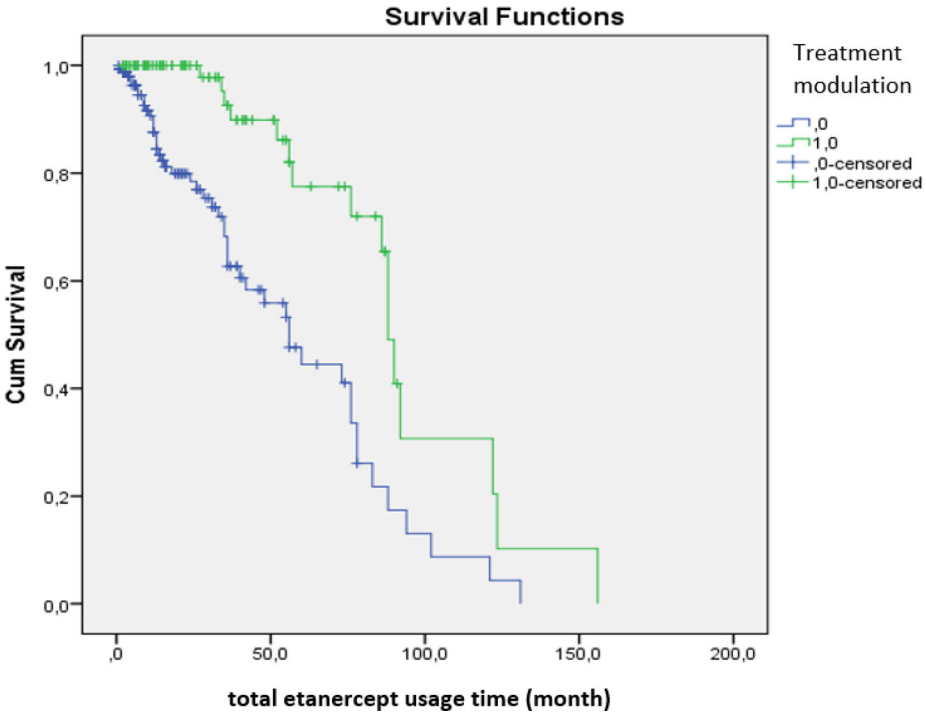


FIGURE 4 Kaplan-Meier survival curve 1. 0, no treatment modulation; 1, treatment modulation

conventional agent (methotrexate or acitretin) to the treatment regimen increased the survival time of the drug[18]; Lie et al also reported that co-medication with a conventional drug resulted in a better retention time.[19] Heiberg et al also reported that psoriatic arthritis patients showed longer retention when etanercept was administered in combination with methotrexate.[20]

To determine the treatment-related behaviors of 64 patients undergoing treatment with etanercept during the COVID-19 pandemic, we contacted the patients by telephone. We successfully reached 57 of the 64 patients. While 41 patients (72%) continued treatment without interruption, 16 patients (28%) terminated the treatment for several reasons, namely crowded workplaces (n = 6), concerns about safety (n = 5), difficulty in accessing the drug (n = 4) and undergoing a cardiovascular operation during the pandemic (n = 1).

SARS-CoV2 infection was confirmed by PCR in one patient who had contact with an infected person. This patient did not require hospitalization and recovered with treatment at home. The patient stopped etanercept treatment for 1 month during this time.

Although the number of patients was small, the results presented here suggested that etanercept does not increase the severity of COVID-19. Haberman et al performed a study in patients with immune-mediated inflammatory diseases (IMID) taking five different anti-cytokine therapies (Janus kinase inhibitor, TNF, interleukin [IL]-17 blocker, IL-23 blocker and IL-12/23 blocker), and suggested that baseline use of biologics was not associated with worse COVID-19 outcomes. No specific results were reported regarding etanercept and psoriasis.[21] Conti et al reported a case series of four psoriatic patients treated with biologics who had a risk of contact with COVID-19 patients.[22] All of these patients were elderly (aged >60 years) and had concomitant diseases, such as hypertension, diabetes, chronic renal failure or previous myocardial infarction. These patients were being treated with guselkumab, adalimumab, secukinumab and ustekinumab. The patients using secukinumab and adalimumab were not tested for COVID-19 and stopped treatment only during the quarantine period, without any worsening of psoriasis. Patients with rheumatological diseases using immunosuppressive drugs, including biological therapy, have been considered to be

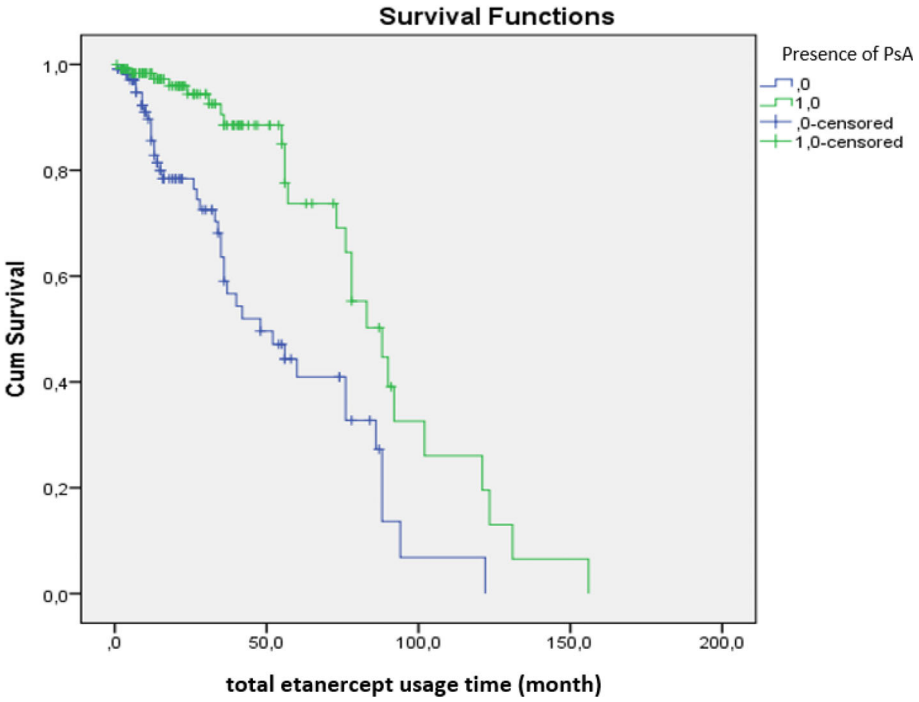
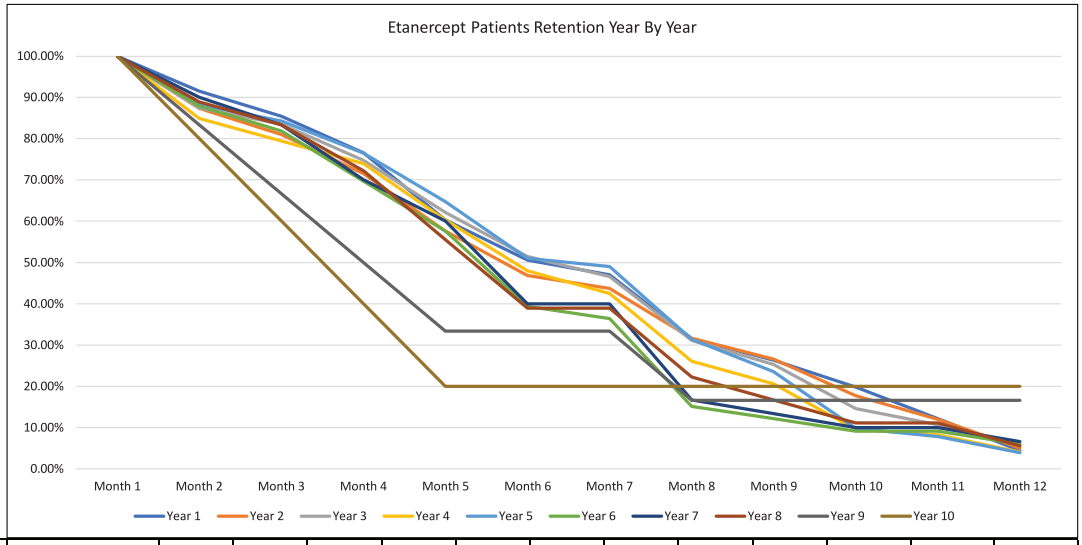


FIGURE 5 Kaplan-Meier survival curve 2. 0, absence of PsA; 1, presence of PsA



	Overall etanercept survival rate	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Year 1	**100.00%**	100.00%	91.50%	85.43%	76.52%	60.32%	50.61%	46.96%	31.58%	26.32%	19.84%	12.15%	4.45%
Year 2	**63.97%**	100.00%	87.34%	81.01%	71.52%	57.59%	46.84%	43.67%	31.65%	26.58%	17.72%	12.03%	5.06%
Year 3	**41.70%**	100.00%	87.38%	83.50%	74.76%	62.14%	51.46%	46.60%	31.07%	25.24%	14.56%	10.68%	5.83%
Year 4	**29.55%**	100.00%	84.93%	79.45%	73.97%	60.27%	47.95%	42.47%	26.03%	20.55%	9.59%	8.22%	4.11%
Year 5	**20.65%**	100.00%	88.24%	84.31%	76.47%	64.71%	50.98%	49.02%	31.37%	23.53%	9.80%	7.84%	3.92%
Year 6	**13.36%**	100.00%	87.88%	81.82%	69.70%	57.58%	39.39%	36.36%	15.15%	12.12%	9.09%	9.09%	6.06%
Year 7	**12.15%**	100.00%	90.00%	83.33%	70.00%	60.00%	40.00%	40.00%	16.67%	13.33%	10.00%	10.00%	6.67%
Year 8	**7.29%**	100.00%	88.89%	83.33%	72.22%	55.56%	38.89%	38.89%	22.22%	16.67%	11.11%	11.11%	5.56%
Year 9	**2.43%**	100.00%	83.33%	66.67%	50.00%	33.33%	33.33%	33.33%	16.67%	16.67%	16.67%	16.67%	16.67%
Year 10	**2.02%**	100.00%	80.00%	60.00%	40.00%	20.00%	20.00%	20.00%	20.00%	20.00%	20.00%	20.00%	20.00%

FIGURE 6 Retention rates for etanercept over time

potentially at risk of COVID-19 infection and complications thereof. Cytokine storm was suggested to be associated with the immunopathogenesis of COVID-19 infection; this involved TNF, which has pro-inflammatory activities that can lead to extensive tissue damage. Certain cytokines that play roles in the pathogenesis of psoriasis, such as TNF-α and IL-17, are increased in inflammatory responses to coronavirus and viral pneumonia. It has been suggested that anti-TNF-α or anti-IL-17 drugs may be beneficial with respect to the

COVID-19 cytokine storm and acute respiratory distress syndrome (ARDS).[23]

In immune-mediated diseases, the risk of severe infection may be associated with chronic inflammatory processes and the use of immunosuppressive drugs.[24] However, case reports have indicated that there is a mild form of COVID-19; anti-TNF agents seem to provide protection against the evolution to more severe forms, and prevent the damaging effects of the high levels of cytokines associated with the immunopathogenesis of infection.[21-25]

5 | CONCLUSION

In this study, patient adherence and the survival rate of etanercept decreased over time. The main reasons for drug discontinuation were loss of efficacy, side effects and patient dissatisfaction. The drug retention rate at 10 to 15 years was 2%.

The use of anti-TNF drugs for immune-mediated diseases may be associated with increased risk of severe infections. However, case reports, including our cases, showed that biologic drugs could protect against the onset and evolution of infectious diseases, such as COVID-19. The COVID-19 pandemic is still ongoing, and further studies and observations are needed to increase our knowledge of this disease.

ACKNOWLEDGMENTS

The authors are grateful to Önder Yildirim and Başak Özkan for their support with patient registration and the recording of data.

CONFLICT OF INTEREST

N. Onsun has served as an investigator for Abbvie, Eli Lilly, Janssen, Novartis and Pfizer, and sat on the advisory boards of Abbvie, Janssen, MSD, Eli Lilly and Novartis in Turkey. The remaining authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Nahide Onsun was involved in the evaluation of patients, design of study, writing original draft, and supervision. Begüm Güneş was involved in design of study and data collection. Ayşegül Yabacı was involved in statistical analysis. All authors provided feedback and helped shape the research, analysis and manuscript.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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How to cite this article: Onsun N, Güneş B, Yabacı A. Retention and survival rate of etanercept in psoriasis over 15 years and patient outcomes during the COVID-19 pandemic: The real-world experience of a single center. *Dermatologic Therapy*. 2021;34:e14623. https://doi.org/10.1111/dth.14623