Etanercept: overview of clinical experience in the treatment of psoriasis and psoriatic arthritis

Biologics have revolutionized the management of psoriasis and psoriatic arthritis. Etanercept was the first biologic to be approved in Europe for the treatment of psoriatic arthritis in 2002 and since 2005 has been approved for the treatment of psoriasis as well. This provides approximately 8 years of experience in the treatment of psoriasis, nearly a decade, which prompted us to review the available data with a special focus on dermatology and compare it with other existing treatment modalities. The aim of this article is to give an update on etanercept with emphasis on information that is important for practical daily use. Most data are based on high-quality studies and official guidelines but, if necessary, data from recent publications or clinical expertise have also been added.

KEYWORDS: biologics ▪ dermatology ▪ etanercept ▪ fusion protein ▪ psoriasis ▪ psoriatic arthritis ▪ safety ▪ therapeutic use ▪ therapy ▪ TNF-α ▪ TNF inhibitor

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Psoriasis is one of the most common skin diseases, affecting approximately 2–3% of the Caucasian population. Plaque psoriasis, the most frequent type, is characterized by sharply demarcated erythematous scaly plaques typically located at the extensor side of the arms and legs, the head and the lower back. Nail involvement such as pits and oil drops is commonly present. Approximately 20% of patients develop an affection of the joints (psoriatic arthritis) [1,2] and 40–60% of them show a progressive course resulting into severe deformation and debilitating erosive arthropathy [3,4]. In addition, psoriasis has been associated with disorders of the metabolic syndrome such as obesity, diabetes, dyslipidemia and cardiovascular disorder, indicating the systemic character of the disease [5–7]. A chronic and often life-long disease, psoriasis is associated with a significant physical and psychological burden affecting all facets of the patient's life and, therefore, profoundly impairs their quality of life [8]. Additionally, psoriasis as well as psoriatic arthritis causes a huge socioeconomic impact [9–12]. All this underlines the high need for effective and safe long-term treatments.

The invention of biologics augmented therapeutic options to a great extent and revolutionized treatment modalities. Therefore, several guidelines for systemic treatments of psoriasis have been developed [13–15]. Concerning psoriasis, biologics are regarded as second-line therapeutics in Europe. They can be used when other conventional systemic treatments are ineffective, contraindicated or cause adverse reactions. This is different in the USA, where biologics might be used as first line if systemic treatment is warranted [15]. Etanercept (ETA), the first approved biologic for the treatment of psoriasis in Europe, is now in use for psoriasis, especially psoriasis arthritis, treatment for nearly a decade and, therefore, a firmly established treatment.

Overview of the market

Psoriasis is a chronic and life-long disease that frequently requires long-term treatment. Although many patients benefit from traditional systemic therapies, unrestricted long-term administration has been limited due to the potential of cumulative toxicity such as renal or hepatic dysfunction or malignancy. In order to diminish the risk of toxicity, physicians have adopted various treatment approaches (e.g., rotational, sequential, intermittent and combination). However, these approaches may not provide continuous disease control or a stable treatment regimen. The recent introduction of targeted biological therapeutics such as ETA, infliximab (IFX) and adalimumab (ADA) offer physicians and their patients treatment options with improved safety profiles, possibly enabling continuous disease control [16].

Until now three classes of biological therapies have been approved for the treatment of psoriasis: the T-cell inhibitors alefacept and efalizumab, the TNF inhibitors and a new substance targeting p40, the common subunit of IL-12 and -23.

Four TNF antagonists (IFX, ADA, ETA and recently golimumab [GO]) have been approved for the treatment of plaque psoriasis and/or psoriatic arthritis. Some substances have been

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approved for the treatment of other indications such as rheumatoid arthritis or Crohn's disease as well. IFX, ADA and GO are monoclonal antibodies against TNF whereas ETA is a fusion protein. Certolizumab, a pegylated Fab-fragment of an anti-TNF antibody, has been approved for use in Crohn's disease and rheumatoid arthritis and is currently in clinical development for the treatment of psoriasis [17].

Although TNF antagonists act in a similar way they show different clinical profiles due to subtle differences in terms of mechanism of action as well as pharmacokinetics and pharmacodynamics. ETA seems to have a more physiological mechanism of action compared with other TNF antagonists as it mimics the fast reversible regulation of TNF naturally occurring by means of the soluble TNF receptor (TNFR)2 [18].

Introduction to the compound

TNF is considered to be an important proinflammatory cytokine in a complex inflammatory network. It is thought to play a role in innate immunity as well as adaptive immunity. While low tissue levels of TNF-α are thought to have beneficial effects such as augmentation of host defence mechanisms against infections, high concentrations may lead to excess inflammation and organ injury. A variety of cells including macrophages, T cells, mast cells, NK cells, fibroblasts and keratinocytes are able to produce TNF. A variety of stimuli induce TNF production, mainly by post-transcriptional regulation.

TNF alters monocyte differentiation, induces the production of a variety of chemokines and adhesion molecules, stimulates T-cell proliferation and promotes T-cell apoptosis and the termination of immune responses by activation-induced cell death as well.

The biological response of TNF-α is mediated through two structurally distinct receptors (TNFR1 and TNFR2). Most biologic activities of soluble TNF (sTNF) are mediated through TNFR1, which is constitutively expressed on all cell types except erythrocytes [19].

The significance of TNF in psoriasis and psoriatic arthritis has been shown by increased levels of TNF-α in lesional psoriatic skin, increased TNF-α mRNA expression in peripheral mononuclear cells of psoriatic patients and increased plasma concentration levels of the bioactive trimeric molecule in psoriatic patients. But most importantly, the application of TNF inhibitors is highly effective to ameliorate the disease activity as shown by many clinical trials and use in daily practice [20,21].

Etanercept is a genetically engineered fusion protein composed of a dimer of the extracellular portions of human TNFR2 fused to the Fc portion of human IgG1, whereas the other TNF inhibitors are full-length bivalent IgG monoclonal antibodies (IFX, ADA and GO) or a monovalent Fab antibody fragment covalently linked to polyethylene glycol (certolizumab). All substances have the potential to bind to TNF-α and inhibit its various functions.

Pharmacodynamics

Etanercept binds to sTNF by interacting with a single TNF (sTNF) trimer, generally resulting in small 1:1 complexes [22] and, in contrast to the anti-TNF antibodies which have the potential to cross-link two transmembrane TNF (tmTNF) trimers, it appears that ETA preferentially binds with both receptor arms to a single tmTNF-trimer with little or no potential to crosslink. Mitoma *et al.* reported that ETA did not induce apoptosis and cell-cycle arrest through reverse signaling by tmTNF, while IFX and ADA could use this mechanism to destroy tmTNF-bearing cells [23].

In addition, ETA is the only anti-TNF agent that is known to bind and neutralize a ligand other than TNF, such as lymphotoxin-α3, a member of the lymphotoxin family. The clinical significance of the latter has still to be elucidated [24].

These differences could at least partially explain the differences in efficacy and safety of the distinct TNF inhibitors. However, this issue is still controversial [25].

Pharmacokinetics & metabolism

Etanercept is administered subcutaneously either by syringe or injection pen. The recommended dosages for patients with predominant or isolated psoriatic arthritis are either 1 × 50 or 2 × 25 mg weekly. In patients suffering from extensive plaque psoriasis, ETA is usually initiated with 2 × 50 mg weekly in order to achieve a fast response. After 12 weeks of initiation phase, ETA has to be reduced to the maintenance dosage of 2 × 25 or 1 × 50 mg of ETA weekly.

Etanercept is well absorbed after subcutaneous injection and the absolute bioavailability is approximately 58–63% [24,26,27]. The central volume of distribution is about 7.6 l, while the volume of distribution at steady-state is 10.4 l according to the EMA specification report [28].

Nestorov *et al.* reported pharmacokinetic data from a total of 1300 subjects with moderate-to-severe psoriasis treated with ETA in clinical

studies (Phase II and III) [26]. The pharmacokinetic data of the representative Phase III study and others are presented in TABLE 1.

After single and multiple dosing the drug was absorbed slowly, reaching peak concentrations 2–3 days after dose administration. Similarly, the drug was eliminated slowly, with a low clearance and a relatively long half-life. The half-life is 70 h, with a range of 7–300 h [28]; therefore, an application once or twice a week is possible [29,30]. The trough concentration–time profiles display dose proportionality with concentration in the 50-mg twice-weekly arm being approximately twice as high as the values measured in the 25-mg twice-weekly arm. The concentration–time profiles at steady state were smooth [26].

Recently, a small study demonstrated that ETA administered as a single 50-mg/ml injection was found to be bioequivalent to two injections of 25 mg/ml [31].

It is assumed that after binding of ETA to TNF, the complex is metabolized through peptide and amino acid pathways with either recycling of amino acids or elimination in bile and urine. Therefore, only a small potential for interaction with other medications is anticipated [32]. Studies showed that no clinically relevant interaction exists between ETA and warfarin or digoxin [33,34]. Moreover, it could be shown that the pharmacokinetics of ETA is not altered by the coadministration of methotrexate (MTX) in patients with rheumatoid arthritis [35]. In summary, no clinically relevant drug–drug interactions between ETA and other commonly prescribed drugs have been detected up to today.

Zhou *et al.* identified a positive correlation between age (<17 years) and apparent clearance; by contrast, no apparent impact of aging (>65 years) on ETA clearance was observed [24]. Interestingly, two studies suggested that bodyweight and/or body surface area might be an important covariate for apparent clearance and apparent volume of distribution [36,37]. Furthermore, the pharmacokinetic profile was neither influenced by known heart insufficiency [38] nor terminal kidney insufficiency [39], but formal studies have not been conducted to examine the effects of renal or hepatic impairment on the pharmacokinetics of the drug.

Efficacy data

Clinical efficacy in psoriasis vulgaris

The most established parameter to measure the severity of skin symptoms in psoriasis is the Psoriasis Area and Severity Index (PASI) [40]. In clinical trials, the most commonly used primary efficacy measure is the PASI 75 response, which is the percentage of patients who at a given point in time achieve a reduction of at least 75% in their baseline PASI, and is now widely accepted as treatment goal [15]. As psoriasis has a strong impact on the quality of life of patients, the Dermatology Life Quality Index (DLQI) has been added to assess efficacy. It is a questionnaire to determine the impact of psoriasis on quality of life [41]. The DLQI score ranges from 0 to 30 and a score of 0 or 1 has been proposed as a treatment goal.

In daily practice, it may be useful to define a second set of treatment goals that serve as 'lowest hurdles' (i.e., a minimum efficacy that should be achieved). If these goals are not met, a treatment should be regarded as inefficient and must consequently be stopped and replaced by another treatment option. A PASI 50 response and DLQI of less than 5 have been proposed as a potentially useful minimum efficacy goal [15]. Therefore, only studies using efficacy parameters such as PASI 75/50 response and/or DLQI have been considered for the evaluation of efficacy in this article.

One Phase II trial [42], five Phase III randomized clinical trials (RCTs) [43–47], two Phase IV studies [48,49] and one investigator-initiated trial [50] have been included documenting the efficacy of different dosages of ETA in adults (25 mg twice weekly, 50 mg once or twice weekly) for a period of 3–6 months (TABLE 2). Two RCTs also deliver long-term data up to 54 or 96 weeks, respectively.

Gottlieb *et al.* presented a Phase II study with 112 patients and report a reduction in PASI of at least 75% for 30% of patients (n = 57) receiving ETA 25 mg twice weekly compared with 2% of patients in the placebo group (n = 55) after 12 weeks. After 24 weeks, the reduction in PASI score increased to 56% in the ETA group compared with 5% in the placebo group [42].

Leonardi *et al.* demonstrated in a RCT with 672 patients a PASI 75 response at weeks 12 and 24, respectively, in 14 and 25% (25 mg once weekly), 34 and 44% (25 mg twice weekly) and 49 and 59% (50 mg twice weekly) of patients treated with ETA compared with 4% of patients (week 12) in the placebo group [43].

In another Phase III study with 583 patients, Papp *et al.* demonstrated a PASI 75 response for 34% of patients after 12 weeks of treatment with ETA 25 mg twice weekly subcutaneously. The twice-weekly administration of ETA 50 mg improved the PASI 75 response to 49% at week 12. Continuous treatment with ETA

Table 1. Pharmacokinetic data taken and modified from recent studies.

Parameters	Healthy volunteer single dose 25 mg sc. (n = 26)	Psoriasis single dose 25 mg sc.	RA single dose 25 mg sc. (n = 25)	Psoriasis steady state week 12, 25 mg sc.; q.w. (n = 160)	Psoriasis steady state week 12, 25 mg sc.; b.i.w. (n = 162)	Psoriasis steady state week 12, 50 mg sc. b.i.w. (n = 164)	RA steady state week 24, 25 mg sc. b.i.w. (n = 23)
C_{max} (ng/ml)	1460 ± 720	1100 ± 600	1072 ± 635	1260 ± 611	2470 ± 523	4900 ± 2490	2400 ± 990
T_{max} (h)	51 ± 14	69 ± 34	69.2 ± 33.8	85.6 ± 42.9	60.5 ± 52.7	69.3 ± 48.1	32.1 ± 27.3
C_{min} (ng/ml)				592 ± 466	1470 ± 567	3100 ± 1560	
C_{ave} (ng/ml)				976 ± 555	1910 ± 496	3670 ± 1980	
AUC (mg•h/l)	235 ± 98		201.7 ± 94.3	164 ± 93.2	321 ± 83.4	600 ± 291	143.6 ± 57.2
Half-life (h)	68 ± 19		102.3 ± 30.1				93.7 ± 18.6
Volume of distribution (l)	12 ± 6						18.5
Clearance (ml/h)	132 ± 85		160 ± 80				
Ref.	[32]	[26]	[27]	[26,43]	[26,43]	[26,43]	[27]

The data are derived from psoriasis patients receiving three different dosages (25 mg weekly, 25 mg twice weekly, 50 mg twice weekly) of sc. etanercept at steady-state conditions at week 12. In addition, pharmacokinetic data after a single administration of 25-mg etanercept sc. in healthy volunteers, in patients with psoriasis or RA, respectively, are included as well. Moreover, pharmacokinetic data after twice-weekly dosing of 25-mg etanercept over 24 weeks in patients with RA have been added.
b.i.w.: Twice weekly; q.w.: Once weekly; RA: Rheumatoid arthritis; sc.: Subcutaneous.

25 mg twice weekly increased the number of patients with a PASI 75 response to 45% after 24 weeks [44].

Tyring *et al.* reported on a Phase III RCT with 618 patients. After an initial 12-week, placebo-controlled phase with ETA 50 mg twice weekly, patients continued or switched from placebo to an open-label extension period of up to week 96 with ETA 50 mg twice weekly. At the end of week 12, 47% of the ETA-treated patients compared with 5% of the patients on placebo achieved a PASI 75. For the ETA/ETA group, PASI 75 response was achieved by 60% of patients at week 24; the placebo/ETA group presented PASI 75 response rates of 48% at week 24 [45,51].

Van de Kerkhof *et al.* presented a 12-week, placebo-controlled, Phase III RCT with an open-label extension phase. A total of 142 patients received either ETA 50 mg weekly (n = 96) or placebo (n = 46). A total of 126 patients entered the 12-week, open-label phase receiving ETA 50 mg weekly, which 122 completed. A total of 37.5% of the ETA-treated patients achieved a PASI 75 response at week 12 with a further increase of the PASI 75 response rate to 71.1% at the end of week 24. Only 2.2% of the patients initially receiving placebo achieved a PASI 75 response at week 12, but 44.4% after switching to ETA 50 mg once weekly at week 24 [46].

Sterry *et al.* presented a multicenter RCT with 752 patients suffering from psoriasis with joint involvement. Patients received either ETA 50 mg once weekly (n = 373) or ETA 50 mg twice weekly (n = 379) for 12 weeks followed by a 12-week, open-label extension phase with ETA 50 mg once weekly. At week 12, a PASI 75 response was achieved by 55% from the twice-weekly/once-weekly group compared with 36% from the once-weekly/once-weekly group. At 24 weeks, 70 and 62% presented with at least a PASI 75 response [48].

In another RCT with 903 patients, Griffiths *et al.* compared the efficacy of ETA and ustekinumab in patients receiving either 45 or 90 mg of ustekinumab (at weeks 0 and 4) or ETA 50 mg twice weekly for 12 weeks. At week 12, 56.8% of ETA-treated patients achieved a PASI 75 response [47].

Long-term data

Of special interest are the long-term data. The Phase III trial from Tyring *et al.* mentioned earlier presented efficacy data up to week 96 (Figure 1). The majority of the reported cases (88%) involved the concomitant use of other immunosuppressants. They demonstrated continuous

Table 2. Efficacy of etanercept in clinical controlled trials.

Patients (n)	Dosage	PASI 75 (%)			PASI 50 (%)		PASI 90 (%)		Ref.
		12 weeks	*24 weeks*	*Long term*	*12 weeks*	*24 weeks*	*12 weeks*	*24 weeks*	
160/672	1 × 25 mg	14	25		41	58		6	[43]
57/112	2 × 25 mg	30.0	56.0			77		21	[42]
162/672	2 × 25 mg	34.0	44.0			70		20	[43]
196/583	2 × 25 mg	34.0	45.0		64		11		[44]
352/711 continuously treated group	2 × 25 mg	36.1	54.5	Week 54: 55.7					[49]
96/142	1 × 50 mg	37.5	71.1		68.8	83.3	13.5	42.2	[46]
373 /752	1 × 50 mg	36.0	62.0						[48]
164/672	2 × 50 mg	49.0	59.0		74	77	22	30	[43]
194/583	2 × 50 mg	49.0			77		21		[44]
591/ 618	2 × 50 mg	47	60.0	Week 96: 52	74	85	21	28	[45,51]
347/903	2 × 50 mg	56.8							[47]
22/60	2 × 25 mg		45		68				[50]
Controlled dose									
194/ 583	2 × 50 mg; weeks 1–12 2 × 25 mg; weeks 13–24	49.0							[44]
379 (752)	2 × 50 mg; weeks 1–12, or 1 × 50 mg; weeks 13–24	55	70						[48]
Children									
106/211	0.5 mg/kg bodyweight once weekly	57	Week 36: 69		76	88	27	37	[52]

PASI 50, 75 and 90 responses at week 12 and week 24 are used to present the efficacy of etanercept in clinical controlled trials. If applicable, long-term values have been included.
PASI: Psoriasis Area and Severity Index.

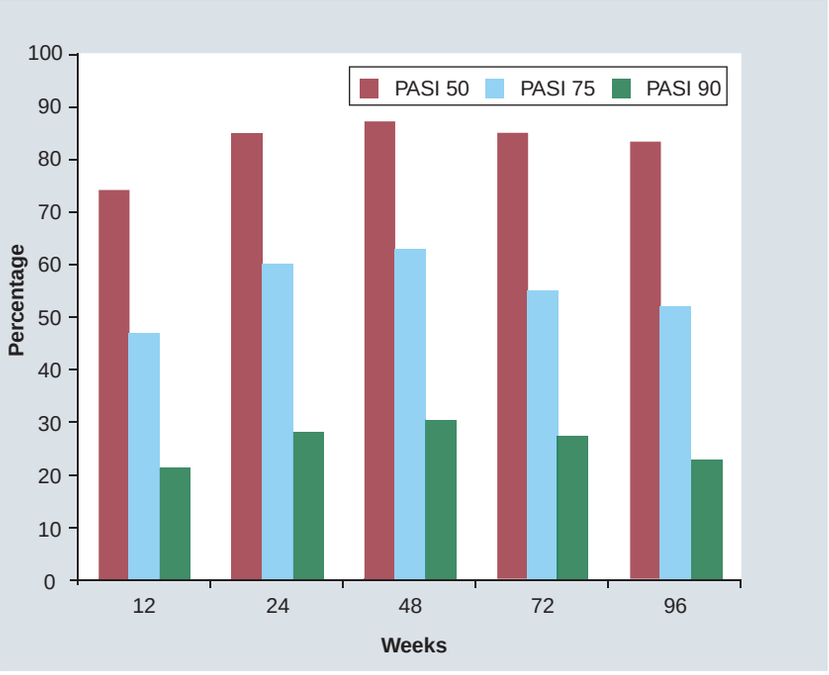

Figure 1. Efficacy documented by Psoriasis Area and Severity Index 90, 75 and 50 response during long-term treatment with etanercept 50 mg biweekly. A total of 618 patients were randomized to either receive placebo (n = 307) or etanercept 50 mg biweekly (n = 311). In total, 597 patients (96.6%) finished the first 12 weeks and 591 (95.6%) entered the open-label extension period. A total of 464 patients (75.1%) completed the study at week 96 [45]. PASI: Psoriasis Area and Severity Index.

improvement up to week 48 with 63% of patients achieving PASI 75 in the ETA/ETA group and 61.1% in the placebo/ETA group. PASI 75 response was maintained throughout week 96 by 52 and 51% of the patients, respectively [45].

Ortonne *et al.* presented a randomized, open-label, multicenter study (Clinical Randomized Year-Long Study Assessing the Safety and Efficacy of Enbrel in Psoriasis [CRYSTEL]) with 720 patients receiving either ETA 25 mg twice weekly (n = 357) for 54 weeks or ETA 50 mg twice weekly for a maximum of 12 weeks or less when the target response of Physician's Global Assessment (PGA) 2 was achieved earlier, followed by treatment pause. Treatment was reintroduced with ETA 25-mg twice weekly only upon relapse to PGA of 3. PASI 75 data are available for patients receiving continuous treatment. At weeks 12 and 24, respectively, 36.1 and 54.5% of the patients from the continuous group achieved a PASI 75 response. This response was maintained until week 54. A total of 72.3% of patients (n = 258) completed week 54 and 55.7% of patients showed a PASI 75 response [49]. At week 54, patients from the continuous group compared with the intermittent group experienced a PASI improvement of 67.5 versus 58.5% [45].

In summary, 30–36% of patients receiving 25-mg ETA twice weekly achieved a PASI 75 response; when treatment was continued until week 24, the PASI 75 response was increased to 44–56%. Other studies conducted more recently showed a better PASI 75 response when patients received 50-mg ETA once a week. A total of 36–37.5% achieved a PASI 75 at week 12 and 62–71.1% at week 24. Using an initial dose of 50-mg ETA twice weekly gave rise to a faster response. A total of 47–57% of patients receiving ETA 50 mg twice weekly showed a PASI 75 response already at week 12. Patients either continuing the dosage of 50 mg twice weekly or reducing the dosage to 50 mg once weekly after week 12 show a further improved PASI 75 response at week 24 between 54 and 70%. These data demonstrate that more than half (up to 70%) of patients benefit greatly from the treatment by achieving a PASI 75 response at week 24. Clinical responses were successfully sustained over 1–2 years. In patients that are in need of a faster response regarding skin lesions, an initial dosage of 50-mg ETA twice weekly for the first 12 weeks is of advantage and advisable.

Clinical efficacy in pediatric patients

Paller *et al.* presented a 48-week RCT with 211 children and adolescents (aged 4–17 years) treated with ETA 0.8 mg per kilogram of bodyweight (maximum ETA: 50 mg per week). They reported PASI 75 improvement at week 12 in 57% of children and adolescents receiving ETA compared with 11% of those receiving placebo. After 36 weeks, 68 and 65% of patients initially assigned to ETA and placebo, respectively, had a PASI 75 improvement [52]. A total of 182 patients were enrolled in a 264-week open-label extension study. Data for week 96 are now available. A total of 140 patients (76.9%) completed week 96. The observed PASI 75 response was 61%. Thus, extended treatment with ETA in pediatric patients showed maintenance of efficacy through week 96 [53].

Improvement in quality of life: DLQI

Four RCTs showed an improvement of the DLQI among the patients treated with ETA (25 mg twice weekly, 50 mg once or twice weekly) ranging from 50 to 70% at week 12 in comparison with 6 and 22% of placebo-treated patients [43,46,51,54]. Van de Kerkhof reported in a trial with patients receiving ETA 50 mg once weekly (n = 96, out of 142) a DLQI improvement of 71% at week 24 [46]. Further analysis showed that a significantly larger proportion of

patients in the ETA 50 mg weekly group achieved an improvement of 5 points in the DLQI (recommended treatment goal in the S3 guideline) compared with those in the placebo group, starting as early as 4 weeks (54.2 vs 31.0%) and continuing through 12 weeks (74.7 vs 28.6%). By week 24, 83.5% of patients who received ETA throughout the study achieved this end point and 72.2% of the patients in the placebo/ETA group. Moreover, at 12 and 24 weeks, 29.2 and 54.4% of the ETA-treated patients achieved a DLQI score of 1 or 0, respectively [55]. Interestingly, Dauden *et al.* presented data from a multicenter, European, open-label study comparing a continuous (n = 352) versus intermittent (n = 359) treatment regime (CRYSTEL study). They showed that both regimes contribute to a statistically significant improvement in quality of life; however, improvement was significantly greater in the continuous treatment group. A total DLQI score of 0 or 1 (signifying no impairment by psoriasis) at week 54 was achieved in 48.9% of patients receiving continuous treatment compared with 26.0% of those who received intermittent treatment [56]. Overall, it can be concluded that the treatment with ETA proved to be efficacious to improve the quality of life in the majority of affected patients. Preliminary data give evidence that in the long-term continuous treatment may be more beneficial than intermittent treatment.

Combination of ETA with other therapies

Although highly effective as monotherapy, in high-need patients a combination with a conventional systemic agent or UV therapy may enhance efficacy and/or allow drug sparing. Furthermore, combination may result in faster treatment response or permit safe transitioning from one systemic agent to another. Evidence to date, especially regarding long-term efficacy and safety, are still limited and need further elucidation.

Most data are available regarding the potential combination of ETA and MTX. Zachariae *et al.* reported a 24-week, randomized, open-label study with 59 patients to evaluate the effectiveness of combining ETA with continued MTX treatment (n = 31) and of ETA with MTX tapered (n = 28) for plaque psoriasis. The combination therapy was significantly superior compared with the tapered regime with 79.9 versus 62.8% at week 18 and 76.4 vs 51.3% at week 24 with comparable safety results [57]. Safety data in rheumatoid arthritis patients taken from the TEMPO study did not show significant differences concerning the safety during a 2 year follow-up period [58]. Therefore, combination with MTX may be a useful option to optimize efficacy in high-need psoriasis patients or may allow dose reduction.

Acitretin is another possible candidate for combination with biologics as it is not immunosuppressive and may act synergistically without increased risk of toxicity. Gisondi *et al.* presented a trial with 60 psoriasis patients receiving either ETA 25 mg twice weekly, acitretin (0.4 mg/kg bodyweight daily) or ETA 25 mg once weekly plus acitretin (0.4 mg/kg bodyweight daily). At week 24, PASI 75 response was achieved by 45% of patients in the ETA group, 30% in the acitretin group and 44% in the group treated with ETA plus acitretin. A combined therapy with ETA 25 mg once weekly and acitretin (0.4 mg/kg bodyweight daily) was more effective than acitretin alone and as effective as ETA 25 mg twice weekly [50].

The combination with UV therapy is another option to enhance treatment response. In a 12-week, single-arm, open-label study, Kircik *et al.* analyzed the efficacy of ETA 50 mg twice weekly plus narrow-band UVB thrice weekly in 86 patients. At week 12, 26.0% achieved PASI 100, 58.1% achieved PASI 90 and 84.9% of patients achieved PASI 75 [59]. Combination of ETA and UVB treatment showed a very fast response in over 80% of patients and might be an option in patients in high need for fast response. However, at present there are only limited data available concerning long-term safety, such as the potential of this combination to increase the risk of skin cancer [60]. Currently there exists insufficient evidence to recommend the combination of narrowband UVB phototherapy with ETA; a RCT would be needed to further investigate this option [14]. For combined treatment with broadband UVB and TNF antagonists, Gambichler *et al.* report a possible increased risk of photocarcinogenesis by influencing apoptotic as well as antiapoptotic pathways [61].

In contrast to MTX, there are limited data on the use of cyclosporine in combination with ETA. Recently, a small study with seven psoriasis patients receiving a combination of ETA 50 mg weekly and tapered low-dose cyclosporine (200 mg/day) has been reported. The combination was effective in these patients, resulting in reduction of the mean PASI following induction therapy (mean: 6.85 weeks) and maintenance therapy (mean: 56.5 weeks) by 94.9 and 93.2%, respectively. Although no safety concerns were raised in this study, the additional immunosuppression must be taken into consideration [62].

Clinical efficacy in psoriasis arthritis

Mease *et al.* presented the results from two RCTs with patients suffering from psoriatic arthritis. In the first trial 60 patients with psoriatic arthritis received either 25-mg ETA twice weekly or placebo. In week 12, 73% of ETA-treated patients achieved an American College of Rheumatology (ACR)20 response compared with 13% of placebo patients [63]. A second trial included 205 patients, receiving 25 mg ETA twice weekly for treatment of psoriatic arthritis. At week 12, 59% of ETA patients achieved the ACR20 compared with 15% of placebo patients and results were sustained until 24 and 48 weeks [64]. Mease *et al.* also investigated the radiographic progression in patients with psoriatic arthritis using a modification of the Sharp method. ETA was seen to be effective in inhibiting radiographic progression throughout 2 years of treatment. Mean adjusted change in total Sharp score were equal to -0.28 units at 1 year and -0.38 units at 2 years [65].

In the Psoriasis Randomized Etanercept Study in Subjects with Psoriatic Arthritis (PRESTA) mentioned above, Sterry *et al.* analyzed the ACR response as well. At week 12, 66.4, 44.7 and 20.3% of patients, respectively, achieved an ACR20, ACR50 and ACR70 response in the twice-weekly/once-weekly group. After 24 weeks, 69, 51.8 and 34.6% of patients achieved ACR20, ACR50, and ACR70 responses. Comparable results were found for the once-weekly/once-weekly group, with 60.8, 40.6 and 21.9% at week 12, and 71.7, 53.6 and 36.7% of patients achieving ACR20, ACR50 and ACR70 responses at week 24 [48]. Interestingly, in contrast to the significant difference in skin response with higher doses of ETA, both doses showed similar results in improving psoriatic arthritis. ACR responses at week 12 are presented in Figure 2.

In summary, twice-weekly administration of 25-mg ETA for 12 and 24 weeks, respectively, resulted in an ACR20 response in 59–73% and 57% of treated patients. At week 24, 40% of patients achieved an ACR50 response. Radiographic progression was shown to be inhibited in a 2-year trial. In addition, quality of life significantly improved in 83 [63] and 54% [64] of the ETA-treated patients measured by the Health Assessment Questionnaire.

Improvement of nail psoriasis

Reports regarding the efficacy of ETA on psoriatic nails remain limited. Luger *et al.* presented a multicenter RCT with 720 patients receiving either ETA 25 mg twice weekly (n = 357) for 54 weeks or ETA 50 mg twice weekly for a maximum of 12 weeks and then intermittent treatment as needed. A total of 79% of the patients had nail psoriasis with a baseline score of 4.64 at the target nail. At week 12, Nail Psoriasis Severity Index (NAPSI) scores decreased to 3.30, an improvement of 28.9%. At week 54, an improvement in NAPSI of 2.38 (51%) was observed. A total of 30% of patients with nail psoriasis at baseline showed a complete clearing at the end of treatment. The NAPSI improvement at week 54 was better in the continuous group (56.5%) compared with the intermittent group (43.5%) [66].

Discontinuation of ETA

There is no evidence of loss of efficacy with interrupted therapy. The majority of patients regained response after re-treatment [67,68]. Therefore, ETA is suitable for intermittent therapy. However, Moore *et al.* report greater improvement with continuous treatment [68], and Dauden *et al.* report in the CRYSTEL study significantly greater improvement in quality of life in patients receiving continuous ETA compared with intermittent application [56].

Safety & tolerability of ETA

In evaluating safety data several aspects have to be taken into account. First, although RCTs are the gold standard to evaluate drug efficacy, they often lack the power to evaluate specific adverse events (AEs) due to the limited number of patients and the duration of follow-up, especially when dealing with issues of uncommon and multifactorial events such as cancer. Second, trials include selected patient populations that do not necessarily reflect real patients in clinical practice. On the other hand, large-scale prospective observational studies are limited due to the lack of randomization and, therefore, the results may be biased by other confounders. Finally, the majority of data are available from other indications and, therefore, may not be directly conferred to psoriasis patients due to differences in comorbidities or concomitant use of other medications [68]. Facing these problems we first present data available for TNF inhibitors in general and then try to focus on safety data directly concerning psoriasis patients receiving ETA as long-term treatment whenever possible. The current data on ETA safety come from clinical studies in several indications such as psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and juvenile arthritis as well as from postmarketing experience.

The collected data are reassuring, but due to the important role of TNF-α as a cytokine of innate immunity, a possible impairment of the surveillance against malignancies and infections has always been a matter of concern.

Infections in general & serious infections

Regarding treatment with TNF inhibitors, data from clinical trials indicate that infections are common, but overall infection rates are not greater than with placebo. However, meta-analyses of clinical trials and registry data produced conflicting data about the possible risk of serious infections (TABLE 3). Askling *et al.* reviewed randomized clinical trials and observational studies regarding the risk of serious infections in patients exposed to anti-TNF therapy in rheumatoid arthritis [69]. In most RCTs no statistically significant differences in the occurrence of serious infections were seen, while a few trials reported an increased risk of serious infections [31,70,71]. Postmarketing observational studies reported either no increase [72,73] or up to a doubled risk [74–76] of serious infections. Recently, Galloway *et al.* (British registry) reported that the adjusted rate of serious infections was 20% higher in the anti-TNF cohort than in the disease-modifying antirheumatic drug (DMARD) cohort; it was highest in the first 6 months of therapy and then decreased over time. Although the crude serious infection rate was found to be highest with IFX, followed by ADA and ETA, the adjusted analysis showed no significant difference in serious infection rates between the three anti-TNF agents [77].

However, Salliot *et al.* retrospectively compared the incidence of infections during the first TNF-blocker course with the incidence during the period before such therapy in the same patient and reported infections in 34.5% of treated patients compared with 6.7% before treatment. These infections are more frequently observed with IFX (50.5%) than with ETA (34.2%) or ADA (15.3%). The serious infection rate of ETA was 4%, which was lower than ADA and IFX [78].

Infections under ETA treatment in psoriasis patients

Tyring *et al.* showed no increase in the incidence of infections among psoriasis patients treated with ETA 50 mg twice weekly subcutaneously compared with patients receiving placebo and/or to the general population during an observation period of 96 weeks [45].

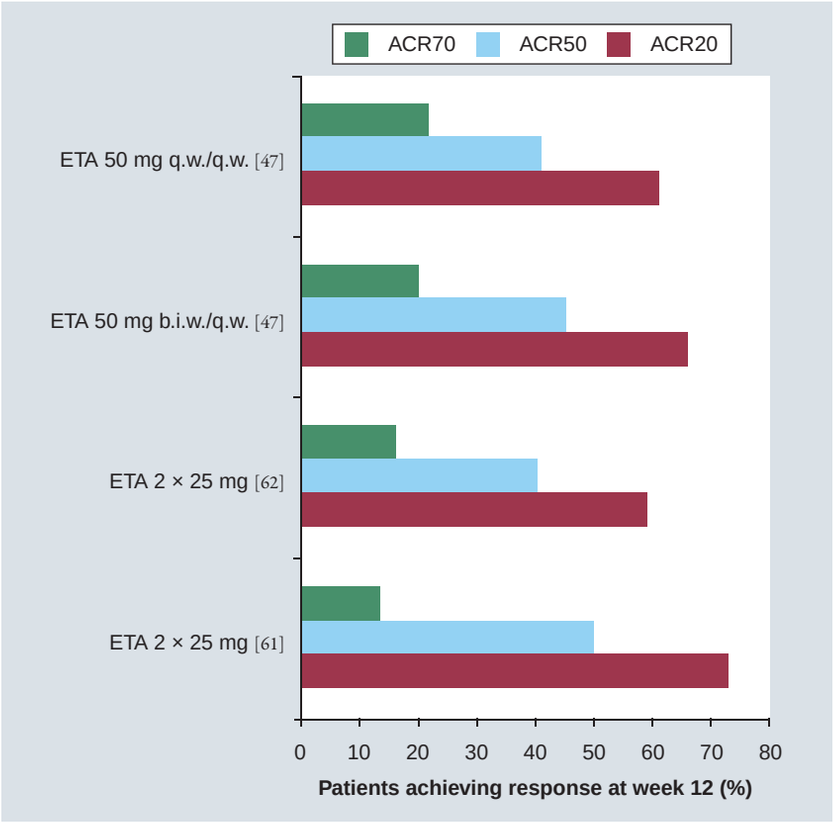

Figure 2. Percentage of patients achieving ACR20, ACR50 and ACR70 responses at week 12.
ACR: American College of Rheumatology; b.i.w.: Twice weekly; ETA: Etanercept; q.w.: Once weekly.
Data taken from [48,63,64].

In an analysis of prospective data from 506 psoriasis patients and an observational period of up to 4 years respectively 1305.4 person-years with exposure to ETA ranging from 50 to 100 mg per week, Papp *et al.* showed good tolerability with no evidence of cumulative toxicity, increase in AE, serious AE, infectious AE or serious infections [79]. Furthermore, rates of myocardial infarction were similar to those in patients with moderate to severe psoriasis [80]. A selection of the occurring AEs with the respective exposure-adjusted rates is listed in TABLE 4.

Paller *et al.* report on an open-label, multicenter, extension trial evaluating long-term treatment with once-weekly ETA at 0.8 mg/kg (maximum 50 mg) in pediatric patients with moderate-to-severe plaque psoriasis and present results after 144 weeks of treatment. A total of 140 out of 182 enrolled patients (76.9%) completed the extension study. A total of 145 patients (80.1%) reported one or more AE, with the most common being upper respiratory tract infections (24.9%), nasopharyngitis (17.1%), streptococcal pharyngitis (12.7%), headache (11.6%) and sinusitis (10.5%). No opportunistic infections

Table 3. Data on serious infections during anti-TNF treatment, modified and taken from registry data and meta-analyses.

Data source	Patients (n)	Serious infections (n)	Serious infections (RR)	Rate per 1000 person-years	Ref.
German Biologics Register	ETA 512 IFX 346	ETA 31 IFX 20	Serious adverse events ETA 2.2 (range: 0.9–5.5) IFX 2.1 (range: 0.8–5.5)	ETA 64 (range: 45–91) IFX 62 (range: 40–95)	[76]
British Biologics Register	7664	525	1.0 (range: 0.7–1.6)	53 (range: 49–58)	[72]
British Biologics Register	8659	737	1.2 (range: 0.9–17)	56 (range: 52–60) ETA: 51.2 ADA: 50.4 IFX: 63	[83]
Swedish Biologics Register	2692	261	1.4 (year 1) 1.2 (year 2) 0.8 (year 3)	54 (47–60)	[69]
US HMO	2393	65	1.9 (range: 1.3–2.8)	16	[75]
US HMO	469	29	1.0	49 (range: 32–70)	[73]
British Biologics Registry	11798 anti-TNF† 3598 DMARDS	1512 296	1.2 (range: 1.1–1.5) 1.8 (range: 1.3–2.6) (6 months)	42 (range: 40–44) 46 (range: 42–50) 43 (range: 39–47) 38 (range: 35–42) 32 (range: 28–36)	[77]
Meta-analysis; 9 RA trials (ADA + IFX)	5014	126	OR: 2.0 (range: 1.3–3.1) OR: 2.3 high dose OR: 1.8 low dose		[100]

†*IFX, ADA and ETA.*
ADA: Adalimumab; DMARD: Disease-modifying antirheumatic drug; ETA: Etanercept; FU: Follow-up; HMO: Health Maintenance Organization; IFX: Infliximab; OR: Odds ratio; RA: Rheumatoid arthritis; RR: Relative risk.

were reported through 96 weeks of the study extension. During 144 weeks of treatment, the types of infections were similar to those reported in adult patients with moderate-to-severe plaque psoriasis [53].

In summary, the risk of infections during treatment with ETA is not fully characterized and differs according to different study and registry data, as well as in comparison with other TNF inhibitors. For daily practice it is important that active infections are seen as absolute contraindication for starting therapy and that patients should be monitored for early signs and symptoms of infection throughout treatment [15].

Soft tissue infections

In the German and British registries, skin and soft tissue infections are more commonly reported with an up to fourfold increased risk [72,76]. However, Askling *et al.* did not find an increased risk in the patient cohort of the Swedish registry [81]. Den Broeder *et al.* presented a large study reporting an increased risk of surgical site infections of up to 50% in patients continued on anti-TNF therapy perioperatively [82], whereas Dixon *et al.* reported that the rate of infections occurring within the first 30 days of surgery does not differ compared with a nonbiologic treated control group [72,83]. Although some authors suggest preoperative discontinuation of therapy [84], there is no consensus in that field. Thus, continuation of the treatment is suggested when disease severity does not allow an interruption.

TB

It is well established that anti-TNF therapy can reactivate latent TB [85].

Rychly *et al.* reported 74 cases of TB per 100,000 patients receiving ETA, and Dixon *et al.* reported 39 events per 100,000. The rate for TB was higher for the monoclonal antibodies ADA and IFX compared with ETA, occurring 3.1- and 4.2-times more frequently, respectively [86–88]. The median time to occurrence of TB was 46 weeks or 13.4 months for ETA in comparison with 30 weeks or 18.5 months for ADA and was lowest for IFX with 12 weeks or 5.5 months [86,88–90].

Table 4. Adverse events that occurred in 506 patients receiving etanercept for a period of up to 4 years.

AEs	Exposure-adjusted rates (events per 100 person-years)	Comments
All AEs	234.5	
SAEs	7.8	
All infections	96.9	
Serious infections (12 in 9 patients; only 3 SAEs [septic shock, fascial infection and myositis] in one patient were considered as possibly related to etanercept)	0.9	No cases of TB or opportunistic infections were reported in the cohort
Nasopharyngitis	26.1	
Upper respiratory tract infection	14.9	
19 malignancies 7 nonskin malignancies (6 patients) 12 nonmelanoma skin cancers (9 patients; 5 BCC, 1 SCC, 3 both) BCC	1.5 0.3	No occurrence of lymphoma in the cohort Incidence of nonskin malignancies was consistent with the expected rate in the general population (SEER database; SIR: 0.91; 95% CI: 0.37–1.88) No statistically significant difference was seen between the observed and expected rates of BCC and SCC with Arizona/Minnesota registries
Cardiovascular events (n = 37)	2.8	
Myocardial infarction	0.6	Rates of myocardial infarction were not different to rates reported from a large population-based cohort of patients with moderate to severe psoriasis
Serious cardiovascular events (n = 22)	1.7	

AE: Adverse event; BCC: Basal cell carcinoma; SAE: Serious adverse event; SCC: Squamous cell carcinoma; SEER: Surveillance, Epidemiology and End Results; SIR: Standardized incidence ratio.
Data taken from [79,80].

Moreover, extrapulmonary or disseminated TB infections are more frequent during treatment with TNF inhibitors. Rychly *et al.* observed extrapulmonary disease in approximately 56% of patients compared with extrapulmonary manifestation in 17.5% of the general population [86]. Dixon *et al.* reported extrapulmonary cases in 62% of patients (25 out of 30), of which 11 were disseminated [88]. Tubach *et al.* reported similar rates: 61% of patients presented with extrapulmonary disease [91]. Data on incidence rates are summarized in Table 5.

Carefully screening for TB and appropriate prophylactic treatment is of the utmost importance. This is underlined by the results of Tubach *et al.* from the prospective French Registry (Research Axed on Tolerance of Biotherapies [RATIO] registry). The sex- and age-adjusted incidence rate of TB was 116.7 per 100,000 person-years in patients treated with anti-TNF therapy. In total, 66.7% of the patients presented with at least one risk factor such as positive tuberculin skin test reaction (≥5 mm), chest x-ray with signs of history of TB or history of or exposure to TB. None of the reported patients had received correct chemoprophylactic treatment [91].

TB screening must be performed as recommended in the local guidelines. A pretreatment chest x-ray and Mantoux skin test currently remain the preferred screening tests in patients not on immunosuppression. IFN-γ release assay (IGRA), such as such as the

Table 5. Annual incidence rates of TB in patients treated with anti-TNF drugs.

	Etanercept	Adalimumab	Infliximab	Cases	Control group	Ref.
TB (IRR)	Referent	4.2	3.1	10,712	3232 (DMARD)	[84]
TB (per 100,000 person-years)	39	144	136	10,712	3232 (DMARD)	[84]
TB (per 1000 person-years)	0.5	0.9	1.5	7664	1354 (DMARD)	[72]
TB (OR)	Referent	17.08	13.29	69	French population	[91]
TB (per 100,000 person-years)	9.3	215	187.5	69	French population	[91]

Annual adjusted incidence rate of TB (per 100,000 patients) based on 57,711 person-years compared with the French population and the annual adjusted incidence rate of TB (per 100,000 patients) based on 23,286 person-years and limited to first anti-TNF drug.
DMARD: Disease-modifying antirheumatic drug; IRR: Incidence rate ratio; OR: Odds ratio.

QuantiFERON®-TB Gold test (Cellistis), is suggested in patients whose Mantoux test result is uncertain. IGRA may be the future gold standard in TB testing [14,15].

Opportunistic infections

There seems to be an increased risk for other intracellular and opportunistic infections including bacteria such as *Legionella*, *Listeria* or *Salmonella* [72,92,93]. In the pooled data of 15,402 patients treated with ETA in clinical trials, the incidence of all opportunistic infections was 0.09% and the exposition-adjusted rate was 0.06/100 person-years [94].

Herpes zoster

Strangfeld *et al.* investigated the risk of herpes zoster in rheumatoid arthritis patients of the German biologics Rheumatoid Arthritis-Observation of Biologic Therapy (RABBIT) registry. The incidence rate of herpes zoster in patients treated with conventional DMARDs was 5.6 per 1000 person-years, which increased to 11.1 per 1000 person-years in those treated with anti-TNF antibodies (ADA and IFX). By contrast, the risk of herpes zoster was only slightly and not statistically significantly increased in patients treated with ETA [95].

Hepatitis B

Reactivation of hepatitis B in chronic carriers of the virus has been reported during treatment with TNF inhibitors. Carroll *et al.* reviewed the literature and found 35 cases with hepatitis B surface antigen (HBsAg) known prior to initiation of TNF inhibitors. IFX was used in 17 cases, ETA in 12 cases and ADA in six cases. All six cases of clinically symptomatic hepatitis were associated with IFX therapy. Therefore, their findings suggest that IFX is associated with a higher relative risk of reactivation of hepatitis B virus in HBsAg-positive patients [96]. Caporali *et al.* investigated the use of TNF blockers in patients with previous but not chronic hepatitis B infection. None of the 67 patients receiving either ETA (n = 23), IFX (n = 25) or ADA (n = 19) developed a hepatitis B virus reactivation, suggesting that anti-TNF-α therapy appears to be quite safe in patients with previous but not chronic hepatitis B infections [97]. Fotiadou *et al.* recently reported a case series of seven patients. All patients were inactive HBsAg-positive carriers with liver function test in the normal range at baseline and received lamivudin 100 mg/day, which started 2 weeks before the initiation of anti-TNF-α medication. Three patients were treated with ADA, three patients with ETA and one with IFX. Liver function tests at the end of the follow-up period were within the normal range. There was no considerable rise in viral load in any of the cases, though one patient receiving IFX showed an increase that reached 600 IU/ml [98].

In summary, according to the literature, ETA and ADA may be safer than IFX in patients with inactive chronic hepatitis B [99]. Successful treatment of psoriasis with anti-TNF-α agents in patients who are inactive HBsAg carriers is possible. However, physicians should consider prophylactic antiviral therapy, and close monitoring for clinical or serological evidence of hepatitis is mandatory.

Hepatitis C

Paradisi *et al.* described three patients with psoriasis and chronic hepatitis C virus infection successfully treated with ETA. When reviewing the literature they identified a further 60 patients either receiving treatment with ETA or IFX, sometimes combined with other immunosuppressants or antiviral treatment. Transaminases or viral load did not change significantly or even decrease, suggesting that anti-TNF treatment can be both safe and effective in patients with chronic hepatitis C virus infection [100].

HIV

HIV is listed among the relative contraindications for anti-TNF-α therapy. However, the safety of TNF-α blockade in the presence of HIV is still unknown. Controlled clinical trials excluded patients with HIV/AIDS; therefore, there are limited published data on the use of TNF blockers in HIV patients. Recently, Barco *et al.* reported a case of successful treatment of a patient with psoriasis and chronic HIV infection with ETA [101]. Domm *et al.* reviewed the literature regarding TNF blockers and HIV. Several case reports have been published where administration of ETA or IFX for various indications did not appear to increase the morbidity or mortality rates in HIV, indicating that their use may be possible in carefully selected patients not responding to other treatment options and being well controlled under antiretroviral therapy. However, these data are limited due to the small sample sizes. Caution must be taken when considering the use of biologic agents in HIV and closer monitoring of these patients is obligatory [102].

Malignancies

With respect to short-term cancer risk, meta-analyses of clinical trial data have indicated the possibility of an increased risk of several types of cancer occurring within months of the initiation of treatment in ADA and IFX, as well as a tendency for an increased risk in ETA-treated patients [103,104]. Additionally, in a trial for Wegener's granulomatosis, six cases of cancer occurred in 89 ETA-treated heavy smokers versus none in 91 comparator patients [105,106]. So far, observational data have not been able to replicate this increase in short-term overall risk of malignancies, but with respect to site-specific risk there exists controversial data, which are presented in Table 6.

Wolfe *et al.* found an increased risk of nonmelanoma skin cancer (odds ratio [OR]: 1.5) and melanoma (OR: 2.3) in patients with rheumatoid arthritis (US cohort, 13,001 patients/49,000 person-years of observation) treated with biologics in comparison with population rates of the Surveillance, Epidemiology and End Results (SEER) database. Whereas no other malignancy (solid tumors or lymphoproliferative malignancies; OR any cancer: 1.0) was associated with biologic use. Furthermore, they found no evidence for an increased incidence of lymphoma in patients receiving anti-TNF therapy when investigating 19,562 patients from the national databank for rheumatic diseases and neither ETA nor IFX was associated with a risk of lymphoma if considered individually [107].

Askling *et al.* presented data from 25,693 person-years of follow-up in 6366 patients newly starting anti-TNF therapy and demonstrated that there was no overall elevation of cancer risk during the first 6 years of anti-TNF therapy and no increase with follow-up time (Table 6) [108].

Mariette *et al.* (French RATIO registry) reported a two- to three-fold increased risk of lymphoma in patients receiving anti-TNF therapy with a 4.73- and 4.12-fold increased risk in ADA- and IFX-treated patients, respectively, compared with patients receiving ETA. However, this rate is similar to that expected for patients with severe inflammatory diseases and, compared with the classic DMARDs, the risk of lymphoma was not increased for any of the three TNF antagonists [109].

Malignancies during ETA treatment in psoriatic patients

Tyring *et al.* saw no increase in the incidence of malignancies in patients treated with ETA over 96 weeks compared with patients receiving placebo and/or the general population [45]. Papp *et al.* also reported no increased risk of malignancies in 506 psoriasis patients treated with ETA for up to 4 years. There was no occurrence of lymphoma or melanoma in this cohort and the incidence of the occurring 19 malignancies (seven nonskin malignancies and 12 nonmelanoma skin cancer) were consistent with the expected rates in the general population (SEER database, Arizona registry) (Table 4) [79].

Recently, ETA has been approved for the treatment of children with psoriasis; therefore, it is of interest to know the safety data concerning children.

Diak *et al.* searched the Adverse Event Reporting System of the FDA to identify malignancies associated with the use of IFX,

Table 6. Summary and comparison of registry data on cancer risk during treatment with the TNF antagonists etanercept, adalimumab and infliximab.

	Etanercept	Adalimumab	Infliximab	Cases	Control group	Ref.
Any cancer (per 100,000 person-years)	743	1202	1020	6604	Swedish population with RA	[108]
Respiratory tract (%)	13	7.7	17	6604	Swedish population with RA	[108]
Gastrointestinal tract (%)	11	15	13	6604	Swedish population with RA	[108]
Reproductive tract (%)	35	39	28	6604	Swedish population with RA	[108]
Urogenital tract (%)	11	3.9	4.2	6604	Swedish population with RA	[108]
Skin (%)	10	7.7	16	6604	Swedish population with RA	[108]
Hematopoietic system (%)	11	15	11	6604	Swedish population with RA	[108]
Other sites (%)	7.1	12	9.7	6604	Swedish population with RA	[108]
RR of a first primary cancer (overall)	0.78	1.32	1.09	6604	Swedish population with RA	[108]
<1 year	0.43	1.91	1.23	6604	Swedish population with RA	[108]
1–2 years	0.8	0.84	0.83	6604	Swedish population with RA	[108]
>2 years	0.92	1.08	1.13	6604	Swedish population with RA	[108]
Lymphoma (OR)	Referent	4.73	4.12	38	French population	[109]

OR: Odds ratio; RA: Rheumatoid arthritis; RR: Relative risk.

ETA and ADA in children and identified 48 malignancies, with half of the malignancies reported being lymphomas. The majority of the reported cases (88%) involved the concomitant use of other immunosuppressants. A total of 15 malignancies were reported following ETA use. The reporting rates for ETA were elevated above background for lymphomas and were similar to background rates for all malignancies [110].

McCroskery *et al.* presented the worldwide experience of ETA use in pediatric patients (estimated 49,176 person-years [4–17 years age group] and 33,887 person-years [18–22 years age group]) and the occurrence of potential malignancies over an 11-year period from 1998 to 2009. In summary, they identified 18 potential malignancies (four leukemia, seven lymphomas and seven solid tumors). The development of a malignancy following ETA is rare, roughly 1.5 cases in 10,000 person-years. The data suggest that there does not appear to be an increased risk of malignancy overall with the use of ETA in children. Among ETA-exposed patients aged 4–17 years, the estimated worldwide and US reporting rates for lymphoma were approximately 0.01 per 100 person-years (one in 10,000 person-years). The estimated relative risk of lymphoma in ETA-treated patients in the 4–17-year-old age group as compared with the healthy US population is approximately 3.8. The expected rate of lymphoma in untreated pediatric patients with juvenile idiopathic arthritis (JIA) or other inflammatory conditions is unknown, although the rate of lymphoproliferative cancers in JIA in the pediatric group has been estimated recently to be 3.8-times the rate in healthy children. Therefore, the risk of ETA in the development of malignancies in children and adolescents is difficult to assess because of the rarity of malignant events, the absence of knowledge of underlying frequency of leukemia and lymphoma in JIA and the confounding use of concomitant immunosuppressive medications [111].

In summary, although it is presently unknown whether psoriasis patients treated with ETA have a higher risk of lymphoma or skin cancer, a potential risk for the development of lymphoma or other malignant diseases cannot be excluded based on current knowledge. Therefore the European S3 guidelines and British guidelines recommend that all patients, particularly those at increased risk of skin cancer at baseline, should be evaluated for skin cancer, both before and during TNF-antagonist therapy. Malignancies in the past are seen as contraindications. The British guidelines add that biologic therapy should be avoided in patients with current or recent history of malignancy unless the malignancy has been diagnosed and treated more than 5 years previously and/or where the likelihood of cure is high (this includes adequately treated non-melanoma skin cancer) [14,15].

Skin reactions: exacerbation of psoriasis

The induction or exacerbation of psoriasis in patients treated with TNF antagonists is a well-established phenomenon. Collamer *et al.* performed a systematic literature review and detected 207 cases of psoriasis exacerbation in patients with rheumatoid arthritis, seronegative spondyloarthropathy or inflammatory bowel disease. Of these, 59% were treated with IFX, 22% with ADA and 19% with ETA. Lesion morphology included pustular psoriasis in 56%, plaque psoriasis in 50% and guttate lesions in 12%; 15% experienced lesions of more than one type. No statistically significant predisposing factors for the development of new-onset psoriasis were found. A total of 66% of patients were able to continue TNF antagonist therapy with psoriasis treatments. Most patients could be managed conservatively without drug withdrawal [112].

Autoimmunity

TNF inhibitors may provoke the development of antibodies due to their protein structure. Papp *et al.* found non-neutralizing anti-ETA antibodies in 1.1% of patients (n = 536) exposed to ETA after 12 weeks of treatment [44]. Other authors, however, report that approximately 5% (2–7.5%) of patients develop antibodies towards ETA. In the summary of product characteristics for ETA in clinical trials for up to 12 months, cumulative rates of anti-ETA antibodies were approximately 7.5% of subjects with psoriatic arthritis and 7% of subjects with psoriasis and 9.7% of subjects with pediatric psoriasis. The relevance of these antibodies is unclear [113]. However, combining ETA with low-dose MTX has been shown to enhance the efficacy [57,114]. In contrast to ETA, antibodies to IFX or ADA were neutralizing *in vitro* and appear to be associated with reduced efficacies of the respective drugs.

De novo development of antinuclear antibodies (ANAs) and anti-dsDNA occurs during therapy with all TNF antagonists. For ETA, ANAs were detected in 10–70% of patients with rheumatoid arthritis and 18%

with psoriasis [15,45]. Anti-dsDNA antibodies developed in 15% of patients with rheumatoid arthritis receiving ETA as compared with 4% receiving placebo [113]. Lupus erythematosus (LE)-like symptoms, however, develop only in a small subgroup of patients [115,116]. In the absence of clinical symptoms, TNF antagonists may be continued regardless of the presence of ANA. From data of a retrospective analysis, De Bandt *et al.* estimate that approximately 0.2% of IFX- and ETA-treated patients develop LE-like symptoms and report that the symptoms resolved either spontaneously or under topical or systemic therapy with glucocorticosteroids after discontinuation of therapy. Relapse of symptoms has not been observed [117].

Injection site reactions during therapy with ETA

Injection site reactions (ISRs) include erythema, itching, pain, swelling and hemorrhage and present the most frequently reported adverse drug reactions for ETA treated patients. ISR occurred in 5–36% for the dose of 2 × 25 mg/week, in 16–18% for 2 × 50 mg and less frequently for weekly doses of 50 mg (14%) or 25 mg (11%). ISR lasted for 3–5 days and were mild to moderate [43,44,64,118]. The reactions occurred mainly in the first months and decreased subsequently. Most patients experienced two or fewer reactions within the first 12 weeks. Only a few patients discontinued treatment because of ISRs [119].

Laboratory abnormalities

In a large study of ETA at different doses, only mild-to-moderate laboratory abnormalities occurred and no patient discontinued therapy due to laboratory abnormalities [120]. Following the recommendations in clinical trials, treatment should be controlled carefully in the case of aminotransferase elevation more than three-times above the upper limit of normal and be discontinued when more than five-times the upper limit. TNF inhibitors are rarely associated with serious leukopenia, neutropenia, thrombocytopenia, pancytopenia or even aplastic anemia. Rare lethal courses of aplastic anemia and pancytopenia occurred within a few weeks after initiation of ETA [121]. In the European S3-guidelines full blood count, liver enzymes, serum creatinine and urine sediment are recommended pretreatment, after 4 and 12 weeks of treatment and thereafter every 3 months [15].

Development or worsening of demyelinizing disease

As a class effect, TNF inhibitors may be associated with development or worsening of demyelinizing diseases such as multiple sclerosis. Although reversible after discontinuation of treatment, TNF inhibitors should not be given in patients with any history of multiple sclerosis or other types of demyelinizing disease because of reports of new onset or exacerbation of multiple sclerosis under treatment with TNF inhibitors [122].

Pregnancy & breast-feeding

Animal studies have not shown any evidence of embryotoxicity or teratogenicity and adverse pregnancy or maternal outcome [28]. However, randomized controlled trials on pregnant women are lacking so far. Therefore, TNF antagonists are classified as category B by the FDA.

Several case reports of female patients exposed to any of the three biologics (ETA, ADA and IFX) around the time of conception exist reporting the delivery of healthy-born infants. However, few cases of miscarriage [123], a prematurely born baby [124] and an incomplete vertebral anomalies, anal atresia, tracheoesophageal fistula, radial and renal anomalies (VATER) syndrome are reported as well [125].

Carter *et al.* presented a review of the FDA database, reporting 61 congenital anomalies in 41 children born to 40 mothers exposed to any one of the three TNF inhibitors mentioned above. These congenital anomalies, mostly part of the 'vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal and limp abnormalities' (VACTERL) spectrum, occurred at a rate higher than expected in historical controls [126].

Ostensen *et al.* show that ETA is excreted in breast milk. However, due to the large size of the protein, the authors question whether oral absorption is possible [127]. Nevertheless it is recommended to avoid breast-feeding during therapy.

In summary, there are reports of successful and complication-free use of TNF inhibitors during pregnancy but these are limited and there are also some reports of perinatal complications including premature birth or association to VACTERL with TNF antagonists. Risk assessment is therefore difficult.

The different guidelines recommend avoidance of pregnancy during treatment with ETA. When pregnancy occurs under treatment with biologics the British guidelines recommend the referral to a specialist fetal medicine unit

and consideration of stopping the treatment. Furthermore, notwithstanding the recommendations of avoiding pregnancy and the importance of contraception in women of childbearing potential, patients should be assessed on a case-by-case basis and the risks to the mother of stopping biologic therapy should be balanced against any potential harm to the fetus or infant [14].

Conclusion

Etanercept has now being used for nearly a decade in the treatment of psoriasis and psoriatic arthritis. Its efficacy has been demonstrated in large clinical trials as well as in daily clinical practice. Furthermore, ETA has shown sustained efficacy over a period of years in a considerable number of patients. Moreover, the short- to medium-term safety is encouraging. However, although certain evidence seems to suggest that ETA may exert a beneficial safety profile with regard to lower rates of TB and herpes zoster in comparison with the anti-TNF antibodies, some important aspects of the safety profile remain unresolved. The prescribing physicians should be aware of a potentially increased risk of serious infections and opportunistic infections. Furthermore, the skin has to be monitored regularly for skin cancer and treating physicians have to consider the still undetermined possible risk of other malignancies, such as lymphomas, particularly in patients with prior malignancies or premalignant states. Further collection of safety information by registries and from postmarketing surveillance is essential for providing information on the absolute risk of long-term and/or rare toxicities.

Future perspective

Approximately 60–70% of patients that do not benefit from standard nonbiologic treatments respond to ETA. However, there are no reliable predictors to determine which patients will or will not respond. Research is ongoing to elucidate possible predictive marker for responders to use them to optimize individualized treatment in the near future. Moreover different treatment strategies may be developed by combining ETA with other treatments to achieve improved efficacy with a better safety profile or by using sequential therapies. The combination of ETA and retinoids has already been investigated in a small pilot trial. Possible options for sequential strategies may include the start of treatment with ETA to effectively correct the proinflammatory state and then change to traditional systemic treatments such as fumaric acid esters or MTX for the long term.

In terms of early treatment, it is possible that systemic treatments will be started earlier in the near future in analogy to the development in rheumatoid arthritis ('hit hard and early'), with the potential benefit to change the natural course of disease and the possibility to be able to stop treatment completely later in the process.

Different new compounds are in the pipeline in order to satisfy the growing demand for safe and effective long-term targeted therapies without compromising the host defence and autoimmunity.

Certolizumab pegol, a pegylated Fab-9 fragment of a humanized anti TNF-α antibody, is a new member in the anti-TNF-α family. Phase II studies for plaque psoriasis showed convincing results, but results of Phase III trials in psoriasis and psoriasis arthritis are pending [128].

For briakinumab, another p40 antibody, good efficacy and safety were shown in a Phase II trial [129]. A Phase III trial for the treatment of psoriasis is ongoing.

Since efficacy data of the monoclonal anti-IL-12/23 antibody has revealed a prominent role of Th17 T-cell differentiation in the pathogenesis of psoriasis, a new monoclonal antibody, which selectively blocks IL-23, will be investigated in the near future. Since only IL-23 is blocked, less immunosuppression is expected.

Similarly, Phase II clinical trials showed good clinical response of rheumatoid arthritis to treatment with a monoclonal anti-IL-17 antibody. Ongoing clinical trials with psoriasis patients treated with a monoclonal antibody against IL-17 are expected to prove the effectiveness of IL-17 blockade in the treatment of psoriasis [130].

For another compound, selectively targeting the JAK/STAT pathway, Phase I and II clinical trials proved efficacy and safety of JAK3 inhibition in preventing transplant rejection and eliminating the symptoms of rheumatoid arthritis and psoriasis. Upcoming results from Phase II and III clinical trials with the small molecule tasocitinib (CP-690550) specifically blocking JAK1/3 will demonstrate efficacy in psoriasis and, therefore, introduce a new generation of immunosuppressive therapies in this field [131]. Similarly, the selective JAK1/JAK2 inhibitor INCB028050 proved efficacy on arthritis without affecting the humoral immunity in murine models. Clinical evaluation of INCB028050 in rheumatoid arthritis has already been launched [132].

Executive summary

Product characteristic/mechanism of action

- Etanercept (ETA) is a TNF blocker. It is a genetically engineered fusion protein composed of a dimer of human TNF receptor 2 fused to the Fc portion of human IgG1 and binds to the soluble TNF-α cytokine, thereby inhibiting its biological function. As TNF plays a central role in the proinflammatory network in psoriasis, inhibition leads to a decrease or even cessation of the inflammatory process.

Pharmacokinetic

- ETA is administered subcutaneously either by syringe or injection pen. The recommended dosages are 1 × 50 mg or 2 × 25 mg subcutaneously weekly. In patients with extensive plaque psoriasis, ETA is usually initiated with 2 × 50 mg weekly doses (over a maximum of 12 weeks) in order to achieve fast response.
- After subcutaneous injection the absolute bioavailability of ETA is approximately 60%.
  - It is slowly absorbed and eliminated with a half-life of approximately 70 h (2–3 days);
  - It is metabolized through peptide and amino acid pathways with either recycling of amino acids or elimination in bile and urine, therefore showing little potential for interactions with other medications;
  - No formal studies have been conducted regarding renal impairment, but terminal renal insufficiency did not impair the pharmacokinetics.

Clinical efficacy

- More than half (up to 70%) of psoriasis patients benefit greatly from the treatment by achieving a Psoriasis Area and Severity Index 75 response at week 24 with sustained clinical responses over 1–2 years. Its use is especially recommended in concomitant joint involvement, as TNF inhibitors can inhibit progression of bone destruction.

Safety

- Good tolerability. Most frequent adverse events are mild injection site reactions and upper respiratory infections. However, the incidence of infections in controlled trials was similar to placebo.
- The safety data are reassuring; nevertheless, the risk of serious infections is still unclear. In addition there are not enough data available to be sure whether psoriasis patients treated with ETA have a higher risk of lymphoma or skin cancer, but a potential risk cannot be excluded.

Drug interactions

- There are no known drug interactions, but due to possible additional immunosuppressive effects, the combination with other immunosuppressants has to be balanced carefully. Combination with methotrexate has been widely used in rheumatology. Combination with anakinra, abatacept and cyclophosphamide is not recommended due to occurrence of potentially serious infections.

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