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CLINICAL REPORT

Tolerability and Safety of Biological Therapies for Psoriasis in Daily Clinical Practice: A Study of 103 Italian Patients

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Studies comparing the safety and tolerability of biological therapies for psoriasis in the long-term and in daily clinical practice are lacking. Most published studies are of selected patients with short-term (3–6 months) follow-up. We performed a retrospective cohort study of 103 patients in order to describe the frequency and the clinical features of adverse events, and to evaluate and compare the tolerability and safety of efalizumab, etanercept, infliximab, and adalimumab in clinical practice. A total of 136 courses of biological therapies were administered, with a mean duration of 16 months/patient; 55 patients received efalizumab, 45 etanercept, 33 infliximab, and 3 adalimumab. Infliximab had an incidence rate ratio of suspension due to severe adverse events 5.9 times (95% confidence interval (95% CI) 1.9–18, $p<0.001$) higher than etanercept and 9.8 times (95% CI 3.2–30.1, $p<0.001$) higher than efalizumab. Safety profiles for efalizumab and etanercept were more favourable than for infliximab. Concerning tolerability, we found that more patients responded to infliximab, but long-term tolerability was higher for both efalizumab and etanercept due to the better safety profile and a higher compliance to therapy. *Key words: psoriasis; adverse events; efalizumab; etanercept; infliximab; adalimumab; tolerability; safety.*

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Psoriasis is a common inflammatory skin condition with an estimated incidence of 2–3% in Europa and North America (1). High-need patients, defined as psoriasis subjects with a moderate to severe condition who have failed to respond to two systemic conventional therapies due to lack of efficacy, intolerance or contraindication, are eligible to receive biological therapies (2, 3). Since the approval of biological therapies, concerns about safety have been raised. Efficacy and safety have been evaluated in many clinical trials conducted on selected patients with a single biological agent, most of them for a short period of time (12–24 weeks) (4–10); however, there is a lack of direct comparison of the tolerability and safety of different biological agents with long-term follow-up, and of reports of experience of the daily management of unselected patients with psoriasis (i.e. reflecting the clinical experience of dermatologists).

METHODS

Objectives

A retrospective cohort study was carried out, which aimed to describe the frequency and clinical features of adverse events in a cohort of patients with psoriasis and psoriatic arthritis who underwent biological therapies from May 2003 to April 2009, and to evaluate and compare the tolerability and safety of biological therapies.

Participants

Case files of 103 patients were reviewed (male:female ratio 64:39, mean age 51.4 years, median age 52 years, age range 14–81 years) followed in the outpatient psoriasis clinics of Florence University (91 patients) and Genoa Galliera Hospital (12 patients) who underwent biological therapies during the period May 2003 to April 2009. Clinical charts were reviewed for demographics, psoriasis characteristics and severity (Psoriasis Area Severity Index (PASI), static physicians global assessment (s-PGA), dermatology life quality index (DLQI)), joint involvement, previous dermatological treatments, biological treatment followed (duration, dosages and adverse events) and concomitant systemic psoriatic treatments (duration and dosages). Patients were visited by the same dermatologist monthly for the first 3 months, then at 2-month intervals. Before treatment initiation, complete blood cell count and routine biochemical analysis were performed, including testing for hepatitis B and C markers, antinuclear antibodies (ANA), anti-DNA antibodies, chest X-rays, and Mantoux test. CBC and routine biochemistry were performed monthly for the first 3 months and then at 2-month intervals during the treatment period. Chest X-rays and Mantoux test were performed yearly and ANA and anti-DNA antibodies every 6 months.

Description of procedures

Adverse events (AE) were classified as mild (MAE: did not required treatment suspension) or severe (SAE: required therapy suspension and/or close monitoring and/or additional systemic therapy and those that resulted in persistent or significant disability or those that were life-threatening).

Flare was defined as typical or unusual worsening of disease during treatment and/or occurrence or new psoriasis morpho-

logies (11). Switch of psoriasis morphology was defined as the emergence of a new type of psoriasis (12). Generalized inflammatory flare (GIF) was defined as the presence of widespread, erythematous, oedematous lesions involving existing plaques.

Immunogenicity was defined as the detection of positive autoantibodies in patients whose baseline autoimmunity status was confirmed as negative (measured by ANAs and ds-DNA antibodies).

Safety and tolerability. Safety assessment was based on the rate of adverse events and the rate of withdrawals due to SAE.

Tolerability assessment was based on the long-term adherence to therapy inversely measured by the overall rate of withdrawals.

Efficacy was measured as a secondary end-point in order to compare adherence to therapy and to assess tolerability. In terms of efficacy, patients were classified into two groups: (*i*) *responders* and (*ii*) *non-responders*; a further quantification of the level of response was beyond the scope of this research. *Responders* were defined as subjects who achieved a PASI-50 response (50% improvement compared with baseline-PASI) or an sPGA score of mild, minimal or clear, or patients who benefited from a quality of life improvement (measured by the DLQI) superior to 50% measured at week-12. *Non-responders* or *lack of efficacy* were defined as patients who did not achieve a PASI-50 response or an sPGA score of mild, minimal or clear, or patients who did not benefit from a 50% improvement in quality of life (measured by the DLQI) within a time period of at least 12 weeks.

Loss of response was defined as a loss ≥ 25% of the best PASI or the best sPGA or the best DLQI values obtained during treatment, measured after the initial 12 weeks of response.

Statistical methods

Standard descriptive statistics, such as mean, median and standard deviations were computed for continuous variables, and rounded numbers (%,) were used for categorical variables. Differences in body weight from day 0 to month 6 within groups were compared with the Wilcoxon's signed rank sum test using Statistical Package for Social Sciences (SPSS) version 12.0 software. All p-values are two-sided and $p < 0.05$ was considered statistically significant. Poisson regression models using Stata, version 10.0 software (Stata-Corp LP, College Station, TX, USA) were used to estimate the incidence rate ratio (IRR) of SAE, of withdrawals due to SAE and to compare the efficacy, tolerability and safety between the different biological therapies. Data for each biological therapy were analysed separately.

For the comparison between malignancy data vs. the general population data, standardized incidence rates (SIRs) were calculated using the ratio of the observed number of cancers to the expected number of cancers for biological therapy. Ninety-five percent confidence intervals (95% CIs) for the SIRs were calculated based on the Poisson analysis (13). The expected numbers of cancers for SIR calculations were based on the Regional Tuscany Cancer Registry, data source: 5-year age-specific cancer incidence rates obtained from the database (2002 to 2006) for all cancers.

RESULTS

A total of 75 patients were affected by psoriasis and 28 patients were affected by both psoriasis and psoriatic arthritis (confirmed by rheumatologist consultation in all cases). Patients were followed for an average of 39 months (range 1–72 months). The mean number of systemic therapies (acitretin, cyclosporine, methotrexate, psoralen plus ultraviolet A (PUVA) and fumaric esters) used in the past was 3.4 (range 1–5, median 3). A total of 136 courses of biological therapies were administered, with a mean duration of 16 months/patient. Fifty-five patients (40%) received efalizumab, 45 (33%) received etanercept, 33 (24%) received infliximab, and 3 (2%) received adalimumab. Twenty-six patients (25%) received more than one biological therapy, though not concomitantly (7 patients (7%) received three and 19 patients (18%) received two biologicals, respectively). Twenty-nine patients (28%) received an additional therapy cycle (re-treatment) after suspension with etanercept (25 patients) and efalizumab (4 patients). The duration and schedule of each treatment are reported in Table I. No statistically significant differences in age, sex and associated comorbidities were present between treatment groups. Some differences in the percentage of patients naïve for biological therapies were noted (infliximab 94% vs. efalizumab 75% and etanercept 65%) (Table I). Being a retrospective study, our patients were treated according the knowledge and the drugs available at that time: 28 patients affected by psoriatic arthritis received only anti-tumour necrosis factor (TNF)-α agents (in 2003 infliximab was the only drug available in our service, in 2004 we started to use etanercept and in 2008 adalimumab). In 2005, our patients affected only

Table I. *Patient numbers (% naïve to biological agents), treatment durations and schedules*

	Efalizumab	Etanercept	Infliximab	Adalimumab
Patients, *n*	55	45	33	3
Naïve, %	75	64	95	0
Treatment duration (months)				
Mean	19.4	17.8	8.7	18.7
Median	12.5	13	8	–
Range	2–46	3–42	1–31	9–34
Dosing	Single conditioning dose of 0.7 mg/kg s.c., followed by 1 mg/kg weekly. Suspended in February 2009 in all 29 patients under treatment according to EMEA recommendation (14).	50 mg s.c. 2/week for 12 weeks, followed by 25 mg s.c. 2/week or 50 mg s.c. 1/week for other 12 weeks until week 24 for psoriasis patients and uninterrupted for psoriatic arthritis. EMEA protocol.	Intravenous infusions of 5 mg/kg/day at week 0, 2, 6 and every 8 weeks thereafter. Premedication with intravenous antihistamine and hydrocortisone.	80 mg at day 0 followed by 40 mg every other week, from week 1 to discontinuation.

EMEA: European Medicines Agency; s.c.: subcutaneously.

Table II. *Monthly incidence rates of adverse events and withdrawals*

	Patients *n*	Monthly incidence rate, %
Efalizumab		
Withdrawal (any reason)	26	2.44
Withdrawal (adverse events)	5	0.47
Adverse events (any)	63	5.92
Serious adverse events	16	0.83
Etanercept		
Withdrawal (any reason)	26	2.91
Withdrawal (adverse events)	5	0.62
Adverse events (any)	40	4.99
Serious adverse events	17	0.95
Infliximab		
Withdrawal (any reason)	29	10.1
Withdrawal (adverse events)	8	2.77
Adverse events (any)	20	6.97
Serious adverse events	16	1.83
Adalimumab		
Withdrawal (any reason)	3	0.32
Withdrawal (adverse events)	2	0
Adverse events (any)	0	0.16
Serious adverse events	1	0

by moderate to severe plaque psoriasis were eligible to receive efalizumab until February 2009, when all 29 patients suspended treatment according to the European Medicines Agency (EMEA) recommendation (14). In April 2009, 19 (42%) etanercept-treated patients, 4 (12%) infliximab-treated patients and one (33%) adalimumab-treated patient were continuing therapy.

Twenty-three (65%) infliximab-treated patients received concomitant therapy with methotrexate (5–10 mg/week) from baseline for the whole period of infusions. In 3 (6%) efalizumab-treated patients cyclosporine therapy at 3 mg/kg/day was added in order to control an inflammatory flare. No concomitant systemic therapy was followed in patients receiving etanercept and adalimumab.

Adverse events

Table II details the monthly incidence rates of adverse events. Infliximab had an incidence rate ratio (IRR) of SAE 3.5 times (95% CI 1.8–6.9, $p < 0.01$) higher than etanercept and 6.2 times (95% CI 3.2–30, $p < 0.001$) higher than efalizumab. Etanercept had an IRR of SAE 1.8 times (95% CI 0.9–3.5, $p = 0.1$) higher than efalizumab, with a non-statistical significant difference.

Table III reports MAE observed in our cohort of patients. Weight gain was evaluated in patients treated for at least 6 months with every single biological agent. Differences in body weight increment were significantly higher among etanercept- and infliximab-treated patients compared with efalizumab-treated patients ($p < 0.001$). The relative risk of gaining body weight among patients exposed to etanercept or infliximab was 14 times higher than in patients exposed to efalizumab (95% CI 3.14–62.46, $p < 0.001$). No significant difference in body weight gain was observed between etanercept- and infliximab-treated patients ($p = 0.1$).

Table IV shows the SAE observed in our cohort of patients. The incidence of neoplasia in our cohort of patients vs. the general population was not significantly greater than 1; SIRs (95% CI) for colon carcinoma 7.13 (0.18–39.73), hepatic carcinoma 35.10 (0.89–195.49), and lung carcinoma 5.92 (0.72–21.37).

Haematological events. As already reported by our group, 4 (5%) of 81 patients who received anti-TNF-α agents developed drug-induced thrombocytopaenia during treatment (15, 16).

Infusion reactions. Interruption of therapy was required in 2 infliximab patients (6%). All the patients who experienced infusion reactions were not following concomitant immunomodulatory therapy.

Arthritis-related adverse events. In our cohort of 1,058 patient-months treated with efalizumab, the frequency of confirmed psoriatic arthritis onset was 22.7 per 1,000 patient-years.

Immunogenicity. Seven patients (21%) developed positive ANA titres (superior to 1/160) during infliximab therapy (6 patients were taking infliximab as monotherapy and 1 patient was under concomitant methotrexate therapy) without other criteria for drug-induced lupus. In two patients the development of human anti-chimeric antibodies (HACAs) was confirmed by the radioimmunoassay detection method (antigen-binding assay).

Tolerability and efficacy

Table V reports in detail the reasons for withdrawal or suspension of therapy. Eighteen patients (17%) sus-

Table III. *Mild adverse events observed in our patients*

	Efalizumab	Etanercept	Infliximab	Adalimumab
Influenza-like symptoms[a], *n* (%)	42 (76)	2 (4)	2 (6)	1 (33)
Injections site reactions[b], *n* (%)	2 (4)	22 (49)	0	0
Mild infections, *n* (%)	1 (2)[c]	1 (2)[d]	1 (3)[e]	0
Weight gain[f], *n* (%)	3 (4)	19 (42)	11 (32)	0
Weight gain (kg), mean ± SD	0.13 ± 0.76 ($p = 0.2$)	1.51 ± 1.95 ($p < 0.001$)	0.93 ± 1.565 ($p = 0.007$)	Not evaluated

[a]Observed within 48 h after the infusion. [b]Defined as local erythema, itching, burning, pain, oedema or urticaria. [c]4 episodes of herpes genitalis.
[d]Bronchitis. [e]Herpes zoster. [f]Evaluated only in patients treated for at least 6 months.
SD: standard deviation.

Table IV. *Severe adverse events observed in our patients*

	Efalizumab *n* (%)	Etanercept *n* (%)	Infliximab *n* (%)	Adalimumab *n* (%)
Serious infections	0	1[a] (2)	1[b] (3)	0
Skin malignancies	2[c] (4)	0	0	0
Invasive malignancies	2[d] (4)	1[e] (2)	1[f] (3)	0
Congestive heart failure	0	0	0	0
Thrombocytopaenia	0	2 (4)	2 (6)	0
Aplastic anaemia or pancitopaenia	0	0	0	0
Neurological events	1[g] (2)	0	0	0
Infusion reactions	0	0	4 (12)	0
Arthritis-related adverse events	2[h] (4)	0	1[i] (3)	0
Immunogenicity	0	2[j] (4)	7[k] (21)	0
Psoriasis flares				
Transient localized papular eruptions	2[l] (4)	0	0	0
Switch of psoriasis morphology	4[m] (7)	1[n] (2)	0	0
Generalized inflammatory flare	3[o] (6)	0	0	0

[a]Disseminated tuberculosis. [b]Recurrent Herpes zoster (4 episodes). [c]One basal cell carcinoma and one in situ melanoma. [d]Two cases of lung carcinoma after 16 and 20 weeks of therapy, in two heavy smokers. [e]One case of colon carcinoma after 23 months of therapy. [f]One case of hepatic carcinoma after 21 months of infliximab + methotrexate. [g]One case of aseptic meningitis. [h]Confirmed psoriatic arthritis after 31 and 56 weeks of therapy. [i]Generalized arthralgia in the context of drug-induced lupus erythematosus (see immunogenicity). [j]One patient was affected by autoimmune thrombocytopaenia. [k]One patient developed drug-induced lupus erythematosus, which completely regressed after 6 months from withdrawal and prednisone therapy. Another patient developed autoimmune thrombocytopaenia. [l]Between the 10th and 15th weeks of therapy. [m]Onset of plaque face psoriasis in two cases and generalized pustular psoriasis in two cases. [n]Onset of palmoplantar pustular psoriasis after 12 months of therapy. [o]Occurred in 3 responders (after 10 weeks, 21 months and 19 months of uninterrupted therapy) not triggered by infections. The GIF was managed successfully in all of the patients without discontinuing efalizumab with a short course of cyclosporine at 3 mg/kg/day, and tapered off once symptoms were under control.

pended therapy due to SAE. Withdrawals were highest between infliximab-treated patients, mainly due to SAE as infusion reactions (6%), immunogenicity (21%) and lack of adherence to therapy (21%). *Lack of efficacy/ non-responders* was the main reason of withdrawal from efalizumab (13%) and from etanercept (22%). *Loss of response* was the most frequent reason for withdrawal from adalimumab therapy (67%). In 2 (6%) infliximab-methotrexate-treated patients the clinical response was diminished, because the interval of response was shortened after 22 weeks and 38 weeks of interrupted therapy and infusions were continued at 6-week intervals.

Infliximab had an IRR of suspension due to SAE 5.9 times (95% CI 1.9–18, $p<0.001$) higher than etanercept and 9.8 times (95% CI 3.2–30.1, $p<0.001$) higher than efalizumab. Etanercept had an IRR of suspension due to SAE 1.7 times (95% CI 0.5–5.8, $p=0.4$) higher than efalizumab with a non-statistical significant difference.

Infliximab was 3.4 times (95% CI 2.1–5.5, $p<0.001$) more efficacious (in terms of *responders* vs. *non responders*) than etanercept and 4.1 times more efficacious than efalizumab (95% CI 2.6–6.4, $p<0.001$); etanercept was 1.2 times more efficacious than efalizumab (95% CI 0.8–1.9, $p=0.4$) but the difference is not statistically significant.

The small sample size of adalimumab-treated patients makes it impossible to compare efficacy, incidence of SAE and incidence of suspension due to SAE with the other biological therapies.

Re-treatment. No loss of efficacy was seen during re-treatment with efalizumab (4 patients) or etanercept (25 patients).

Table V. *Reasons for withdrawal or suspension of therapy*

	Efalizumab *n* (%)	Etanercept *n* (%)	Infliximab *n* (%)	Adalimumab *n* (%)
SAE	5 (9)	5 (11)	8 (24)	0
Lack of efficacy	7 (13)	10 (22)	1 (3)	0
Loss of response	1 (2)	4 (9)	6 (18)	2 (67)
Lost in follow-up	7 (13)	7 (16)	7 (21)	0
Patient request/other	1[a] (2)	1[b] (2)	7 (21)	0

[a]Alcoholism. [b]Pregnancy.
SAE: serious adverse events.

DISCUSSION

High-need psoriasis patients require long-term treatment plans where stable efficacy, safe profile and compliance became essential. Unfortunately, most clinical research worldwide in psoriasis consists in short-term (3–6 months) evaluations in selected patients (4–10, 17, 18). Our study is an attempt to compare the tolerability and safety of efalizumab, etanercept and infliximab in daily clinical practice and for a long follow-up period. In addition a few patients treated with adalimumab were studied. The mean follow-up of our patients (39 months) and the mean treatment duration (16 months/patient) are the longest to our knowledge found in the literature (4–10, 17, 18).

The majority of papers published to date, assess the efficacy and safety of single drugs in selected cohorts of patients; long-term randomized controlled trials that compare the efficacy, tolerability and safety of different biologicals are lacking and only one study, by Warren et al. (4), compares the efficacy and safety of different

biologicals, but without analysing tolerability and adherence to therapy (5–10, 17, 18).

In our patients the safety profiles of efalizumab and etanercept were more favourable than the safety profile of infliximab. In fact, in Europa and North America infliximab had an IRR of SAE 3.5 times ($p < 0.01$) higher than etanercept and 6.2 times ($p < 0.001$) higher than efalizumab. Infliximab frequently causes infusion reactions and immunogenicity, whereas injection site reactions should be considered for etanercept and influenza-like symptoms for efalizumab. Since efalizumab is no longer commercially available the most relevant comparisons can be made between etanercept and infliximab. Immunomodulatory therapy (methotrexate) associated with infliximab reduced the frequency of infusion reactions and immunogenicity (19), improving tolerability. Weight gain was significantly higher among etanercept- and infliximab-treated patients compared with efalizumab-treated patients, in accordance with previous literature reports (20). Drug-induced thrombocytopaenia was more frequent during etanercept and infliximab treatment, therefore immediate monitoring of platelet count is recommended and autoimmunity should be suspected (15, 16). The overall risk of carcinoma was not increased during the course of treatment with biologicals when compared with the general population, as confirmed by different published trials (17, 18). We noticed a higher frequency of efalizumab-associated arthritis events; considering the worldwide reported efalizumab post-marketing surveillance frequency of arthopathies of 4.8 per 1,000 patient-years, our findings (22.7 per 1,000 patient-years) may be over-estimated due to the small sample size (21). In February 2009, EMEA recommended the suspension of marketing authorization for efalizumab due to safety concerns, including the occurrence of progressive multifocal leukoencephalopathy (14); except for one event (aseptic meningitis), no other neurological events were observed in our efalizumab-treated patients. The frequencies of psoriasis flares in our patients are in accordance with reports in the literature (22, 23). GIF has been described in non-responding efalizumab-treated patients during the first weeks of treatment and after withdrawal; however, we reported a 6% frequency not associated with the initial phases of therapy or with discontinuation (23).

Concerning tolerability, we found that more patients responded to infliximab, but long-term tolerability was higher for both efalizumab and etanercept due to the better safety profile and higher compliance with therapy, which may be related to the more convenient route of administration.

The monthly proportion of patients that continued therapy against the monthly withdrawals favoured efalizumab (one monthly withdrawal for every 23.6 patients) and etanercept (1 monthly withdrawal for every 14.5 patients) and was not encouraging for infliximab (1 monthly withdrawal for every 1.2 patients). Considering the low number of adalimumab-treated patients, the proportion 1:104 is mis-estimated. Loss of response was the cause of withdrawal in a higher percentage of patients during adalimumab therapy (67%) compared with efalizumab (2%), etanercept (9%) and infliximab (18%) therapy. No loss of response during infliximab treatment was seen in patients treated concomitantly with methotrexate, but the clinical response was shortened in two cases. We hypothesize that the loss of response seen during infliximab treatment could be associated with the rapid clearance of infliximab due to the development of antibodies (HACAs) in patients not following concomitant immunomodulatory therapy, even if HACAs were not measured in this group of patients (19).

A systematic review and meta-analysis by Schmitt et al. (24) regarding efficacy and tolerability of systemic treatments for psoriasis concluded that there is a significant difference in efficacy between biologicals; infliximab being the most efficacious, followed by adalimumab. Our data confirm indirectly the efficacy outcome of this meta-analysis, despite the fact that in our study efficacy was measured only secondarily in order to assess tolerability. Our experience differs in the safety results: we found a higher monthly incidence of withdrawals due to SAE for infliximab (2.77% vs. 1.3%) and a lower incidence for efalizumab (0.47% vs 1.2%) and etanercept (0.62% vs. 1%). Possible explanations may reside in our smaller cohort size, the unselected type of patients and the different follow-up time. Concerning tolerability, Schmitt et al. (24) reported similar overall rates of adverse events and withdrawals between infliximab, etanercept, efalizumab and adalimumab, but direct comparison between different biologicals was not reported, due to the differences in the duration of individual trials and the lack of key comparative data concerning long-term safety. In our experience, efalizumab and etanercept appear to be better tolerated than infliximab (24).

Warren et al. (4) conducted a case-note review of 102 psoriasis patients treated with infliximab, etanercept and efalizumab to assess efficacy and safety in the clinical setting. These authors reported that all three biologicals were well tolerated, but direct comparison of tolerability rates was not performed (4). Liver abnormalities were reported in 7–20% of patients, suggesting a drug-induced liver hepatotoxicity susceptibility in psoriasis patients (4). These findings were not encountered in our cohort of patients, perhaps due to different alcohol consumption rates between our populations. Unfortunately, to date we cannot compare our tolerability rates with other similar studies because reports of direct comparison between biological agents are lacking.

Being a retrospective study, this work was prone to selection biases; although no statistically significant differences in age, sex and associated co-morbidities

were present between treatment groups, differences in the percentage of patients naïve for biological therapies (infliximab 94% vs. efalizumab 75% and etanercept 65%) were recorded, in addition to therapy selection biases, and these might represent confounding factors. In addition, 21 patients were lost to follow-up. The key limitations of our study are the number of patients and the retrospective design. Moreover, the small sample size of adalimumab-treated patients makes it impossible to compare safety and tolerability with the other biological therapies.

Validation of our data in larger studies is needed, and should be performed with the help of national registries that can collect data prospectively over a long period of time.

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