Drug focus: adalimumab in the treatment of moderate to severe psoriasis

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Abstract: Adalimumab is a fully human IgG1 monoclonal antibody that specifically binds to tumor necrosis factor (TNF)-alpha, and is administered by subcutaneous injection. The mechanism of action is based on both the neutralization of TNF-alpha bioactivity and the induction of apoptosis of TNF-expressing mononuclear cells. The drug is approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis (PsA), and recently also for the treatment of Crohn's disease. The effectiveness of adalimumab in psoriasis was previously suggested by the subset analysis of patients enrolled in PsA trials who were affected by concomitant psoriasis, and recently confirmed by a phase II trial and the preliminary results from phase III trials in moderate to severe psoriasis. These results demonstrate that adalimumab is effective in improving psoriasis and quality of life, with sustained effects over ≥ 1-year treatment period. The safety data from psoriasis studies were similar to those of previous studies in other diseases. The risk of adverse events did not appear to increase with continuous long-term exposure to adalimumab.

Keywords: adalimumab, psoriasis, pharmacokinetics, mechanism of action, efficacy, safety

General aspects of psoriasis

Psoriasis is a chronic inflammatory immune-mediated skin disease that affects 1%–3% of general population. The disease is characterized by hyperproliferation and abnormal differentiation of keratinocytes, vascular changes in the papillary dermis, intraepidermal accumulation of neutrophils and dermal inflammation with prominent lymphocytic infiltrate. The development of psoriasis has a multifactorial nature resulting from the interaction between genetic predisposition and environmental factors. Pathogenic mechanisms are considered to be secondary to an abnormal immune response, with an aberrant regulation of both the adaptative ($CD4^+$ Th1 lymphocytes and $CD8^+$ type-1 T-cells) and the innate immunity (dendritic cells, macrophages, keratinocytes) resulting in a complex network of cytokines, chemokines and growth factors (Gaspari 2006).

Among the different clinical variants, plaque psoriasis is the most frequent, accounting for more than 80% of cases. Psoriatic plaques are papulo-squamous lesions with variable dimensions and degree of erythema, scaling and infiltration. They can be localized or diffuse and are often itchy. Nail involvement is common, especially in patients with concomitant psoriatic arthritis (PsA). PsA is now considered more aggressive than previously thought and has been reported to occur in 6% up to 42% of psoriatic patients, usually after the appearance of skin lesions (Gladman et al 2005). Psoriasis has a relevant influence on quality of life, causing social and physical disability, employment problems, productivity loss, feeling of stigmatization, depression, and other psychological problems. The psychosocial and economic burdens of psoriasis are significant (Kimball et al 2005; Hazard et al 2006; Sohn et al 2006). Overall direct and indirect costs of treating psoriasis are high, especially for patients

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with recalcitrant disease, and are likely to be underestimated. Therapeutic management of psoriasis is complex and requires an individualized approach. The choice of treatment is usually influenced by disease severity, location of lesions, impairment of quality of life, response to previous treatments, presence of concomitant PsA or other comorbidities. Severity of psoriasis can be defined by the Psoriasis Area and Severity Index (PASI) (Fredriksen and Petterson 1978) and the body Surface Area (BSA) affected, which are objective measures used by regulatory agencies and in research setting. Traditional approaches to moderate to severe disease (with PASI at least of 10 and BSA involvement >10%) include ultraviolet light therapy with UVB or with psoralens and UVA (PUVA), and systemic agents, such as cyclosporine, methotrexate (MTX), and acitretin. The use of these approaches can be limited by conditions which contraindicate their use, lack of efficacy, dose-dependent and time-dependent toxicity, or inconvenience. Common problems encountered in clinical practice with the use of traditional therapies are patient's dissatisfaction and non-adherence to the treatment regimen prescribed (Nijsten et al 2005; Christophers et al 2006; Richards et al 2006). Moreover, treatment success does not necessarily correspond to complete clearance and may have no impact on psychological distress (Fortune et al 2004; Feldman et al 2005).

The recent introduction of biologic agents (monoclonal antibodies or fusion proteins) interfering with specific pathogenic targets has widened the possibilities of treating adult patients with chronic moderate to severe disease who are candidates for systemic therapy or phototherapy. Biologic agents currently available for the treatment of psoriasis include drugs which act by binding to T-lymphocyte antigens, eg, alefacept (which is not yet approved by EMEA) and efalizumab, or by targeting tumor necrosis factor (TNF), eg, the fusion protein etanercept and the chimeric monoclonal antibody infliximab. In European countries, biologic agents are approved for the treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or have a contraindication to, or are intolerant to other systemic therapies including cyclosporin, MTX or PUVA. TNF-blockers are also indicated for the treatment of PsA.

The serendipitous discovery of the effectiveness of anti-TNF biologics in psoriasis has suggested the crucial role of this cytokine, which can be implicated in multiple events of psoriasis-related inflammation: attraction of leucocytes into the skin, activation of dendritic cells and T lymphocytes, release of epithelial and vascular growth factors, synthesis of cytokines, chemokines and other proinflammatory mediators via activation of NF-kappaB (Victor et al 2003).

Adalimumab: pharmacological profile

Indications, dosage and administration

Adalimumab (Humira®, D2E7, Abbott Laboratories, Abbott Park, IL, USA) is a fully human IgG1 monoclonal antibody that specifically binds to TNF-alpha. The drug is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kDa.

In most countries, including the U.S. and Europe, adalimumab is approved for treatment of adults with rheumatoid arthritis (RA), PsA and ankylosing spondylitis. The first indication was treatment of RA, for which adalimumab received the approval by the FDA in December 2002. The recommended dosage of adalimumab is 40 mg administered every other week (EOW) as a subcutaneous (s.c.) injection. The use of MTX in PsA is facultative, and, in RA patients not taking concomitant MTX, the dosing frequency can be increased to 40 mg every week to obtain additional benefit. In February 2007, the FDA approved adalimumab to treat adult patients with moderately to severely active Crohn's disease (at the dosage of 160 mg at week 0, 80 mg at week 2, followed by a maintenance dose of 40 mg EOW starting at week 4). On the 2nd of July 2007, adalimumab received the approval for treatment of severe active Crohn's disease also by the EMEA, which recommends the combination with corticosteroids during the induction phase, except for patients who are intolerant to steroids or in whom continued treatment with corticosteroids is inappropriate. At the time of writing this review, adalimumab is in phase III clinical trials for psoriasis and is expected to be approved for the treatment of this disease within the end of 2007.

The drug product is supplied as either a single-use, 1 mL prefilled glass syringe or a single-use, prefilled 1 mL autoinjector (the pen), both providing 40 mg of adalimumab. The two delivery systems are FDA- and EMEA-approved. The pen was developed to facilitate self-injection by patients with physically limiting diseases. Systemic exposure and safety profiles of adalimumab were comparable between the two devices (Paulson et al 2007). A phase II, open-label, single-arm study assessed patient preference of the pen versus the syringe in 52 patients with active RA who had been self-administering

adalimumab 40 mg EOW via a syringe for at least 3 months (Kivitz et al 2006). Overall, 76.9% of patients reported that the pen was less painful than the syringe and 88.5% preferred the pen. The majority of patients considered the pen easier to use (94.2%), more convenient (92.3%), requiring less time to inject (82.7%), and safer (88.5%).

Pharmacokinetics and immunogenicity

Pharmacokinetic studies showed that, after a single 40 mg dose, absorption and distribution of adalimumab appeared to be slow, with an average absolute bioavailability of 64%. The serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40 and 80 mg EOW and every week s.c. dosing, and increased also with concomitant MTX. As compared to RA patients, treatment with 40 mg EOW in PsA patients resulted in a slight increase of mean steady-state trough concentrations. MTX was found to reduce the apparent clearance of adalimumab after single and multiple dosing by 29% and 44% respectively. In long-term studies over two years, there was no evidence of changes in clearance over time. Population pharmacokinetic analyses revealed a trend toward lower apparent clearance with increasing age and toward higher clearance with increasing body weight and in the presence of anti-adalimumab antibodies (AAA). In fact, the serum levels of free adalimumab (not bound to AAA) were observed to be lower in patients with detectable AAA. Minor increases in apparent clearance were also predicted in patients receiving doses lower than the recommended dose. The real clinical relevance of these findings is still unknown. Pharmacokinetic features of adalimumab are summarized in Table 1.

The long-term immunogenicity of adalimumab is not known, although the drug is thought to be less immunogenic than the chimeric monoclonal antibody infliximab. In three randomized RA trials, approximately 5% of 1062 patients receiving adalimumab developed low-titer AAA at least once during treatment, which were neutralizing in vitro. The incidence of antibodies was greater at lower doses than at higher doses and among patients receiving EOW doses versus weekly doses (Anderson 2005). In RA patients, concomitant MTX therapy was associated with a reduced incidence of AAA formation as compared to adalimumab monotherapy (1% versus 12%). In patients with ankylosing spondylitis and PsA, the rate of development of AAA was comparable to patients with RA, although in PsA patients receiving concomitant MTX the rate was higher than that observed in RA patients (7% versus 1%). In patients with Crohn's disease, the rate of AAA development was 2.6%. There was no apparent correlation of AAA development to adverse events, in terms of both frequency and pattern. In RA patients receiving the recommended dosage of 40 mg EOW as monotherapy, no significant difference in clinical response rate at week 26 was detected between AAA-positive patients and AAA-negative patients (van de Putte et al 2004). However, the evaluation of the influence of AAA on the clinical response had produced contradictory results so far. A recent study investigated the prevalence of AAA development and their clinical relevance in a cohort of 121 consecutive RA patients treated with 40 mg EOW (Bartelds et al 2007). AAA were detected in 21 patients (17%) during 28 weeks of treatment. High concentrations of AAA were associated with non-response to adalimumab therapy, as well as with lower serum adalimumab concentrations. Interestingly, restoration of clinical response after the increase of dosing frequency in patients who were previously non-responders was associated with the disappearance of AAA.

The data regarding the immunogenicity of adalimumab are dependent on the sensitivity and specificity of the different assays used to detect AAA which are not standardized. Moreover the reported rate of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, underlying disease, concomitant medications, and especially the concentration of adalimumab in the serum. In fact, the presence of adalimumab may interfere with the assay so that patients with high serum concentrations of the drug are expected to have AAA undetectable. This means that the actual incidence of AAA can be underestimated and that high levels of AAA are more likely to be detected when adalimumab concentrations are absent or low (Bartelds et al 2007; Bender et al 2007).

Awaiting more information about the clinical significance of AAA, useful hints can be suggested by taking into account the current knowledge on the immunogenicity of infliximab (Vena and Cassano 2007). Development of anti-infliximab antibodies has been reported in 14% to 61% of patients treated with infliximab; antibody detection was found to be inversely related to the dosage of infliximab and more frequently associated with maintenance treatment with episodic infusions as compared to regular scheduled infusions every 8 weeks. Anti-infliximab antibodies can increase the clearance of infliximab (Rojas et al 2005), thus causing a more rapid decline of serum concentrations of the drug. Positivity of anti-infliximab antibodies does not preclude clinical responsiveness, although it can influence the rate of sustained response in the long term. In clinical practice, when response to infliximab is reduced, it can be restored through dose

Table 1 Synopsis of pharmacokinetic features of adalimumab[a]

Bioavailability	64% (single 40 mg dose)
C_{max}[b] (mg/L)	4.7 ± 1.6 (single 40 mg dose) 7.7 ± 3.4 (steady state, 40 mg EOW[c])
T_{max}[d] (hours)	131 ± 56 (single 40 mg dose)
AUC (mg h/L), steady state	1830 ± 850 (40 mg EOW)
Vss[e] (L)	4.7–6.0
Mean steady-state levels (mg/L)	5 (40 mg EOW without MTX[f])8–9 (40 mg EOW with MTX). Higher with higher doses and slightly higher in PsA[g] (6–10 mg/L without MTX and 8.5–12 mg/L with MTX)
Half-life (days), single dose	10–20 (mean, 2 weeks)
Systemic clearance (L/h)	0.012 Apparently reduced with concomitant MTX by 29% (after single dosing) and 44% (after multiple dosing). Possibly lower with increasing age (ie, in patients aged 40 to >75 years) Possibly higher: – with increasing body weight – in patients receiving doses lower than the recommended dose – in the presence of AAA[h]

[a]Data reported in Humira® Prescribing Information (FDA - label approved on 26/02/2007; EMEA – Rev. 7, published on 02/07/07); [b]Cmax, maximum serum concentration; [c]EOW, every other week; [d]Tmax, time to reach the maximum concentration; [e]Vss, distribution volume; [f]MTX, methotrexate; [g]PsA, psoriatic arthritis; [h]AAA, anti-adalimumab antibodies.

escalation (Rutgeerts et al 2006) which can counteract the loss of stable serum concentrations of infliximab. The concomitant use of MTX or other immunosuppressants has been reported to reduce the incidence of anti-infliximab antibodies, but it is not recommended in psoriasis. Recently, a study carried out in RA patients disclosed that levels of anti-infliximab antibodies were only slightly reduced by concomitant MTX and were not influenced by other antirheumatic drugs or prednisone (Bendtzen et al 2006).

Pharmacodynamics and mechanism of action in psoriasis

The mechanism of action of adalimumab is primarily linked to the neutralization of TNF-alpha bioactivity by preventing the interaction of TNF-alpha with the cell surface TNF receptors. Through this mechanism, adalimumab inhibits several TNF-alpha-induced events, ie, the release of serum cytokines (IL-6), acute phase reactants of inflammation, matrix metalloproteases and other markers of cartilage and synovium turnover, and the expression of adhesion molecules responsible for leukocyte migration (Mease 2005).

Like infliximab, adalimumab lyses TNF-expressing cells in the presence of complement. The induction of apoptosis in activated mononuclear cells, via activation of intracellular caspase, is considered a relevant mechanism in Crohn's disease treatment (Shen et al 2005, 2006). Instead, the exact role of apoptosis in the mechanism of action of TNF-blockers in either rheumatic diseases and psoriasis is still unknown.

In a study of 64 RA patients, treatment with adalimumab caused no signs suggestive of depression of delayed-type hypersensitivity and immunoglobulin levels, as well as no change in counts of T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils (Mease 2005).

A recent study gave interesting hints to elucidate the pathophysiological role of Langerhans cells in psoriasis and to understand the mechanism of action of adalimumab (Gordon et al 2005). A significant reduction in the absolute number and density of epidermal Langerhans cells was discovered in untreated psoriatic skin as compared to uninvolved skin from psoriatic patients. The depletion of Langerhans cells appeared to be specific for psoriatic plaques and was not detected in nonpsoriatic skin lesions characterized by hyperkeratosis, including nonimmune-mediated conditions, such as seborrhoeic keratoses, or lichen planus which is an inflammatory skin disorder associated to the secretion of type I cytokines. Results obtained in the mouse xenograft model suggested that the decrease in epidermal Langerhans cells is an early event during plaque formation. Effective treatment with adalimumab in psoriatic patients restored the density of epidermal Langerhans cells in lesional skin, supporting that these cells may have an antiinflammatory role and are crucially involved in the physiological differentiation of keratinocytes. The increase of Langerhans cells was already evident within 7 days of adalimumab treatment, when clinical response was not yet evident.

Clinical trials of adalimumab in psoriasis

Preliminary data from PsA studies

All TNF-blockers, including adalimumab, were investigated in rheumatic diseases prior to psoriasis, so that the first data

documenting the potential effectiveness in psoriasis were suggested by the subanalysis of the effect on concomitant skin lesions in patients enrolled in PsA trials.

The Adalimumab Effectiveness in PsA Trial (ADEPT) study was a phase III, 24-week, randomized, parallel-group, placebo-controlled, double-blind study which evaluated the efficacy and safety of adalimumab in patients with moderately to severely active PsA who had a history of inadequate response or intolerance to non-steroidal anti-inflammatory drugs (Mease et al 2005). MTX use was permitted during the study only if it had been taken for at least 3 months previously and was maintained at a stable dosage for a minimum of 4 weeks before treatment start. A total of 315 patients were randomized to receive s.c. injections of placebo (n = 162) or 40 mg adalimumab (n = 151) given EOW for 24 weeks. Nearly half of the patients in both groups were receiving MTX at baseline. In brief, the cumulative results showed that, as compared to placebo, adalimumab significantly improved the signs and symptoms of PsA and the physical-related functional disability, and inhibited the radiographic progression of arthritis. The response of PsA to adalimumab was rapid and sustained throughout the 24-week treatment period and did not differ between patients treated with adalimumab as monotherapy and those receiving concomitant MTX.

The influence of adalimumab treatment on concomitant skin lesions was considered a secondary efficacy endpoint in patients whose psoriasis involved at least 3% of the BSA. A total of 138 patients (69 patients in each group) underwent skin assessment. Evaluation of these patients was performed using the PASI, and the physician's global assessment (PGA), as well as the Dermatology Life Quality Index (DLQI) (Finlay and Khan 1994). PASI response was rated as the proportion of patients who exhibited at least a 50%, 75% or 90% improvement of PASI from baseline (PASI 50, PASI 75, and PASI 90, respectively). Significant differences in the PASI response rates between the active treatment and placebo groups were evident as early as week 4. At week 12, the PASI 50, PASI 75 and PASI 90 responses were obtained in 72%, 49% and 30% of patients (compared with 15%, 4%, and 0% in the placebo-treated patients), respectively. The results achieved with adalimumab were sustained at week 24, when patients who met the PASI 50, PASI 75 and PASI 90 response criteria were 75%, 59%, and 42% (versus 12%, 1% and 0% in patients receiving placebo), respectively. PASI improvements were independent on the severity of baseline psoriasis and did not differ between patients who had mild to moderate psoriasis (PASI <10) or moderate to severe disease (PASI ≥ 10) at baseline. Results of the PGA showed that 67% of patients receiving adalimumab therapy achieved either 'clear' or 'almost clear' ratings by week 24 (as compared to 10% in the placebo group). Clinical results were paralleled by DLQI improvement, with a mean change from baseline of –6.1 versus –0.7 in the adalimumab-treated patients compared with the placebo group. A complete resolution of skin-related functional improvement (DLQI = 0) was achieved in 43.6% of patients receiving adalimumab therapy versus 5% of those treated with placebo by week 24 (Gladman et al 2007a).

Patients who completed the 24-week double-blind phase of ADEPT were eligible to enter an open-label extension trial with s.c. adalimumab, 40 mg EOW, until the drug was commercially available and for a maximum of 120 weeks. Patients who failed to achieve at least a 20% improvement in both swollen and tender joint counts after at least 12 weeks of the open-labeled treatment could be treated with adalimumab 40 mg given every week. Clinical results at week 48 have been recently published and showed the sustained effect of adalimumab at a dosage of 40 mg EOW on clinical and radiographic outcomes of PsA, as well as on PASI responses, regardless of the use of concomitant MTX (Gladman et al 2007b). Patients who required dose escalation on or after week 36 were 15 in the group treated with adalimumab in the blinded phase (total n = 138) and 23 of the 147 patients from the original placebo arm. Moreover, continuous treatment with adalimumab 40 mg EOW led to a sustained improvement of skin lesions through week 48, when the mean PASI improvement from baseline was 68% and the PASI 50, PASI 75 and PASI 90 responses were observed in 67%, 58% and 46% of patients, respectively. Notably, at week 48, 33% of these patients were completely cleared (= PASI 100 responders). Patients treated with placebo during ADEPT achieved a 64% mean improvement in the PASI score after 24 weeks of the open-label adalimumab therapy, which allowed the achievement of the PASI 50, PASI 75, PASI 90 and PASI 100 response rates of 61%, 53%, 44%, and 31%, respectively. Patients with psoriasis who underwent dose escalation on or after week 36 were 8 of the 69 patients from the adalimumab trial and 12 of the 59 patients from the placebo arm. Subsequent post-hoc subanalyses of ADEPT showed that the clinical efficacy of adalimumab against PsA and psoriasis at weeks 24 and 48 did not vary according to PsA duration at baseline (Choy et al 2007) and that the PASI 100 response was associated with a better dermatology-related quality of life than PASI 75–99 response as defined by the proportion of patients with DLQI of 0 or 1 (95% versus 68%) (Gladman et al 2007c).

Psoriasis studies

The results of a phase II, 12-week, randomized, double-blind, placebo-controlled study (M02-528) with adalimumab in 147 patients with moderate to severe psoriasis have been recently published (Gordon et al 2006). The publication also included the results of a subsequent 48-week extension phase (M02-529). Eligible patients included adult patients with moderate to severe plaque psoriasis of at least 1-year duration and involving 5% or more of their BSA. Patients who had been treated with anti-TNF treatment were excluded. Concomitant psoriasis therapies were not allowed with the exception of low- to mid-potency corticosteroids applied topically to the palms, soles, face, and groin. In the initial study, patients were randomized 1:1:1 to receive s.c. injections of: a) 80 mg of adalimumab at week 0 followed by 40 mg EOW from week 1 onward; b) 80 mg of adalimumab at weeks 0 and 1 followed by 40 mg per week; or c) placebo weekly from week 0. Patients who completed this initial trial were eligible to continue in the extension trial, in which patients who received adalimumab during the initial study continued their assigned dosages, whereas placebo group was switched to 80 mg of the active drug at week 12, and 40 mg EOW beginning at week 13. In weeks 13–24, patients remained blinded to the frequency of adalimumab therapy. In the subsequent open-label phase (weeks 25–60), patients in the placebo/EOW and EOW groups were eligible for dosage escalation (to adalimumab 40 mg per week) if they had less than PASI 50. Patients who required dose escalation were regarded as non-responders in the primary analysis.

A statistically significant improvement in mean PASI score occurred as early as week 1 and a higher percentage of PASI 50 responders in both the adalimumab treatment arms was observed by week 2 as compared to placebo. Clinical response rates did not appear to be influenced by sex, age, or body weight of patients and by baseline severity of psoriasis. After 12 weeks of treatment, 53% of patients who received 40 mg of adalimumab EOW and 80% of patients who received 40 mg/week of adalimumab achieved the PASI 75, compared with 4% of patients treated with placebo. The response to adalimumab was sustained through week 60 in the majority of patients. Details of PASI response rates over the study period are shown in Table 2.

Between weeks 24 and 60, 34 patients (18 from the placebo/EOW group, 12 from the EOW group, and 4 from the weekly group) did not achieve the PASI 50 response and were therefore eligible for dose escalation. Among the 30 patients from the placebo/EOW and EOW groups, PASI 50 and 75 rates at week 60 were 40% and 17%, respectively. This suggests that dose escalation may restore response in some patients. It would have been interesting to have data about the development of AAA and adalimumab serum concentrations and to correlate these aspects to clinical response, but these findings were unfortunately not available for this study.

The sample size analyzed and the open-label design of a portion of the extension phase did not allow reliable assessment of data about the efficacy of EOW versus weekly treatment. However, the results seem to indicate that the weekly dosing was more rapid for the achievement of meaningful responses (PASI 75 up to PASI 100) at week 12 and was associated with greater PASI 90–100 rates at week 60 than EOW dosing.

A subgroup analysis of this phase II trial revealed that long-term adalimumab treatment caused a meaningful improvement of quality of life whose magnitude appeared to be dependent on the response rate (Gordon et al 2007). In fact, at week 60, patients with PASI $<$50, 50–74, 75–99, and 100 had mean reductions from baseline in DLQI of 6.0, 8.8, 11.5, and 11.1, respectively. At week 60, a DLQI score of 0 was achieved by 0%, 28%, 37%, and 79% of patients with PASI $<$50, 50–74, 75–99, and 100 responses, respectively. After the completion of the extension M02-529 trial, patients entered in a phase III open-label extension study (M03-658) which evaluated the long-term efficacy and safety of continuous administration of adalimumab 40 mg EOW (Papp et al 2007). Among patients who continued to be treated (n = 49), PASI responses were generally maintained up to week 120.

Results from randomized controlled phase III trails of adalimumab in moderate to severe psoriasis have recently presented and are summarized in Table 3. The M03-656 (REVEAL) study confirmed the effectiveness of treatment with adalimumab 80 mg at week 0 and 40 mg EOW from week 1 to week 15 versus placebo (Menter et al 2007). Efficacy was sustained during open-label treatment with adalimumab. At week 33, PASI 75 responders were re-randomized to continue adalimumab 40 mg EOW or receive placebo treatment up to week 52. During this period, 28.4% of subjects receiving placebo experienced a loss of adequate response (defined as either a response less than PASI 50 relative to baseline or a $\geq$ 6-point increase in PASI from weeks 34 to 52 relative to week 33) compared to 4.9% of patients still receiving adalimumab. The CHAMPION study compared for the first time a biologic agent (adalimumab) with a traditional systemic drug (MTX) in patients with moderate to severe chronic plaque psoriasis (Saurat et al 2006). Adalimumab demonstrated significantly superior efficacy versus MTX and versus placebo.

Table 2 Phase II trial of adalimumab in moderate to severe psoriasis (M02-528 and M02-529 studies): response rates

Visit	Response[a]	Placebo/Adalimumab 40 mg EOW[b] (% of patients)	Adalimumab 40 mg EOW (% of patients)	Adalimumab 40 mg per week (% of patients)
Week 12	PASI 50	NA[c]	76	88
	PASI 75	4	53	80
	PASI 90	NA	24	48
	PASI 100	0	11	26
Week 24	PASI 75	55	64	72
	PASI 100	11	13	24
Week 36	PASI 75	57	62	68
	PASI 100	19	22	36
Week 60	PASI 50	57	64	66
	PASI 75	45	56	64
	PASI 90	40	33	48
	PASI 100	19	16	26

Patients in the placebo group were switched to adalimumab 40 mg EOW at week 12.
[a]Response defined as the improvement of the Psoriasis Area and Severity Index (PASI) of at least 50% (PASI 50), 75% (PASI 75), 90% (PASI 90) and 100% (PASI 100) from baseline; [b]EOW, every other week; [c]NA, not available.

Table 3 Randomized controlled phase III trials of adalimumab in moderate to severe psoriasis: Synopsis of study characteristics and efficacy results

Study/Reference	Patients and study design	Efficacy results
M03-656 (REVEAL[a]) /Menter et al 2007	A multicenter, 52-week, randomized study in 1,212 patients with a diagnosis of plaque psoriasis for at least 6 months, and with a PASI[b] ≥12, and affected BSA[c] ≥10%, all naïve to anti-TNF[d] therapy Three sequential phases: • Period A (16 weeks) – double-blind, placebo-controlled phase; 2:1 randomization to: – adalimumab 80 mg at week 0 and 40 mg EOW[e] thereafter (n = 814) – placebo (n = 398) • period B (17 weeks) - open-label phase in patients with PASI 75[f] response at week 16: n = 580 in the adalimumab group (who continued to receive 40 mg EOW), and n = 26 in the placebo group (who began adalimumab 80 mg at week 16 followed by 40 mg EOW) • period C (19 weeks) - double-blind, placebo-controlled phase in PASI 75 responders at week 33; 1:1 randomization to: – adalimumab 40 mg EOW (n = 250) – placebo (n = 240)	Period A – PASI 75 response for adalimumab – at week 8: 54.1% (vs 3% for placebo); – at week 12: 67.7% (vs 4.8% for placebo); – at week 16: 71% (vs 6.5% for placebo) Period B – Mean PASI improvement achieved at week 16 was maintained through week 33 Period C – Loss of adequate response[g] for adalimumab (vs placebo): 4.9% (vs 28.4%)
CHAMPION[h]/ Saurat et al 2006	A multicenter, 16-week, randomized, double-blind double-dummy, placebo-controlled study in 271 patients with a diagnosis of psoriasis for at least 1 year, and with a PASI ≥ 10 and affected BSA ≥ 10%, all naive to both anti-TNF treatment and MTX[i] 2:2:1 Randomization to: – adalimumab 80 mg at week 0, followed by 40 mg EOW (n = 108); – oral MTX 7.5 mg at weeks 0 and 1, 10 mg at weeks 2 and 3, and 15 mg from week 4 onward (n = 110); the weekly dose was reduced in case of safety problems from week 2 until week 15, or increased to 20 mg at week 8, and 25 mg at week 12 if PASI 50 was not achieved in the absence of safety concerns – placebo (n = 53)	PASI 75 response for adalimumab – at week 8: 62% (vs 13% for placebo and 9% for MTX); – at week 12: 77% (vs 15% for placebo and 25% for MTX); – at week 16: 80% (vs 19% for placebo and 36% for MTX)

[a]REVEAL, Randomized Controlled Evaluation of adalimumab Every other week dosing in moderate to severe psoriasis triAL; [b]PASI, Psoriasis Area and Severity Index; [c]BSA, body surface area; [d]TNF, tumor necrosis factor; [e]EOW, every other week; [f]PASI 75, PASI improvement of at least 75% from baseline; [g]Loss of adequate response defined as either response < PASI 50 relative to baseline or a ≥6-point increase in PASI at weeks 34–52 relative to week 33; [h]CHAMPION, Comparative Study of HUMIRA vs Methotrexate vs Placebo In PsOriasis PatieNts; [i]MTX, methotrexate.

Other considerations about treatment with adalimumab in psoriasis

Rheumatologic experience has suggested that switching to adalimumab can restore a good clinical response in patients with loss of efficacy from other anti-TNF biologics, infliximab or etanercept, over time (Wick et al 2005). Adalimumab treatment was also found to be beneficial for patients with Crohn's disease who experienced loss of response or intolerance to infliximab (Sandborn et al 2004).

Preliminary data from small series of psoriatic patients show that adalimumab can be effective for patients whose psoriasis was refractory to infliximab and etanercept and can reestablish the PASI 75 response in patients who did not maintain this level of response after step-down dosing of etanercept from 50 mg twice weekly to 50 mg weekly (Pitarch et al 2007; Yamauchi 2007).

An ever-growing number of case reports have documented the possible occurrence of psoriasis exacerbation during treatment with TNF-inhibitors, as well as that of new-onset psoriasis or psoriasis-like lesions in patients without history of psoriasis and undergoing anti-TNF therapy for other conditions, especially RA (Cohen et al 2007; de Gannes 2007; Fiorentino 2007; Goiriz et al 2007). These paradoxical phenomena have been reported with all the available anti-TNF-alpha biologics, including adalimumab. Flare of skin lesions in psoriasis patients often involved areas previously unaffected and developed as new clinical variants (eg, flexural psoriasis, eruptive guttate psoriasis, or palmoplantar pustulosis) never presented by patients in their lifetime. The outcome of reactions was variable, consisting of either worsening requiring discontinuation of the anti-TNF, or complete resolution despite continuation of the anti-TNF, often after use of topical anti-psoriasis drugs or other rescue treatments. The mechanisms of these reactions are not known, although several hypotheses may be suggested, such as the involvement of autoimmune phenomena or effector cytokines other than TNF-alpha (including interferon-alpha), the dual opposite effects of TNF-alpha on immune homeostasis and apoptosis, and the triggering effect of infectious factors.

Safety profile of adalimumab

The absence of cumulative organ-specific toxicity of biologic therapies creates the premises for the innovative concept of a long-term continuous treatment to control psoriasis. However, there are other potential safety issues related to biologic therapy. Although the available evidences support the favorable safety profile of biologic agents for psoriasis, long-term follow-up in large sample populations is required to obtain more precise information, particularly about uncommon adverse events. In the meantime, a positive risk/benefit ratio may be preserved through careful selection of patients and monitoring, based on the recommendations of the manufacturing companies and consensus guidelines (Smith et al 2005). Table 4 shows the recommendations reported in the prescribing guidelines of adalimumab.

Due to the importance of TNF in host defense, one of the issue of major concern with all TNF-blockers, including adalimumab, is the increased risk of infections and malignancies (Scheinfeld 2005; Desay and Furst 2006). The most important infectious complication is the reactivation of tuberculosis (TB), whose incidence has decreased following implementation of TB screening (Schiff et al 2006). In post-marketing experience with adalimumab, TB, frequently disseminated or extrapulmonary, and other opportunistic infections have been reported (Orenstein 2006). The overall rate of TB in clinical studies involving over 13,000 patients was 0.26 per 100 patient-years, and 0.07 per 100 patient-years over 4500 patients in the US and Canada. The risk of TB increased with doses of adalimumab higher than those recommended. In placebo-controlled studies, the most common infections were bronchitis, upper respiratory tract and urinary tract infections.

A double-blind, randomized study demonstrated that adult RA patients treated with adalimumab can be effectively and safely immunized with pneumococcal and influenza vaccines (Kaine et al 2007). Percentages of patients achieving a vaccine response were similar in the adalimumab and placebo groups following pneumococcal vaccination and lower with adalimumab than placebo following influenza vaccination. Instead, proportions of patients with protective antibody titers were similar in both treatment groups following each type of vaccination.

The potential role of TNF inhibitors in the development of malignancies is not known. Adverse event reporting and cohort studies have failed to demonstrate any linkage between the development of solid tumors and anti-TNF therapy. Patients with chronic inflammatory diseases, such as RA, are known to be at higher risk for the development of lymphoma, in apparent correlation to longstanding high disease activity. Some evidences indicated that RA patients treated with TNF-blocking agents, including adalimumab, do not have higher lymphoma risks than other patients with RA (Desay and Furst 2006; Schiff et al 2006).

In clinical trials of adalimumab, 12% of treated patients versus 7% of the placebo group developed anti-nuclear antibodies. However, development of a lupus-like syndrome appears to be uncommon during treatment with adalimumab or other anti-TNF drugs. Due to the frequent occurrence of autoantibodies

Table 4 Prescribing information of adalimumab[a]

Contraindications	– Hypersensitivity to adalimumab or to any of the excipients – Active TB[b] or other severe infections such as sepsis, and opportunistic infections – Moderate or severe heart failure (NYHA[c] class III/IV) Treatment should not be initiated in patients with active infections including chronic or localized infections until infections are controlled Not recommended for use in pregnant and breastfeeding women, and in children <18 yrs
To be used with caution in patients with:	– History of recurrent infection – Underling conditions which may predispose to infections, including the concomitant use of immunosuppressive drugs – Chronic carriage of hepatitis B – Pre-existing or recent onset of CNS[d] demyelinating disorders – History of malignancy – Heavy smoking habit (chronic obstructive pulmonary disease) – Mild heart failure (NYHA class I/II) – Previous TB even after adequate treatment
Concomitant treatments not recommended	– Live vaccines – Anakinra
Special recommendations before and during treatment	Before treatment – TB screening (evaluation of risk factors, chest x-ray and tuberculin skin test) – Adherence to local recommendations for the initiation of treatment in patients with TB (if latent TB is diagnosed, appropriate anti-TB prophylaxis must be initiated before starting treatment) – Evaluation of HBV[e] infection During treatment: – Close monitoring of HBV carriers – Close monitoring of infections before, during and after treatment – Avoidance of exposure to risk factors for infections – Close monitoring for signs of heart failure – Contraception in women of childbearing potential Principal reasons for discontinuation of treatment: serious infection, serious allergic reaction, HBV reactivation, lupus-like syndrome, confirmed significant haematological abnormalities, new or worsening symptoms of congestive heart failure.

[a]All data derived from the Humira® Prescribing Information approved by the EMEA (Rev. 7, published on 02/07/07) and by the FDA on 26/02/2007; [b]TB, tuberculosis; [c]NYHA, New York Heart Association; [d]CNS, central nervous system; [e]HBV, hepatitis B virus.

during anti-TNF therapy, they are considered without clinical relevance, unless symptoms suggestive of lupus-like syndrome develop. Therefore, measurement of anti-nuclear antibodies and anti-dsDNA is not required during treatment with TNF-alpha antagonists (Vena and Cassano 2007).

Other safety problems rarely associated with TNF-blockers, including adalimumab, are represented by blood dyscrasias, including thrombocytopenia, leukopenia and pancytopenia, new onset or exacerbation of congestive heart failure and worsening or initiation of multiple sclerosis and other demyelinating disorders (Scheinfeld 2005; Desay and Furst 2006).

Safety data from the psoriasis studies were comparable to those of previous studies of adalimumab in RA and PsA. The overall incidence of adverse events did not differ between adalimumab and placebo, and, in the CHAMPION study, among adalimumab, placebo and MTX groups, and it remained stable over long-term treatment periods up to 120 weeks (Gordon et al 2006; Saurat 2006; Menter et al 2007; Papp et al 2007).

In all studies of adalimumab, the most frequent side effect was injection site reaction, which was generally mild to moderate and transient, and did not require drug discontinuation. In placebo-controlled trials, injection site reactions were reported in 17%–20% of patients treated with adalimumab (versus 11%–14% of patients receiving placebo).

In the ADEPT, elevations in transaminases were more common in adalimumab-treated patients than placebo-treated patients. The majority of these elevations were transient, and occurred primarily in patients who were receiving concomitant hepatotoxic drugs, such as MTX (Mease 2005).

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