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REVIEW

Current status and new developments in the treatment of psoriasis and psoriatic arthritis with biological agents

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Psoriasis is a chronic inflammatory disease affecting 1–3% of the general population. Among psoriatic patients, 5–40% are affected by psoriatic arthritis. Due to the chronic nature of the disease, patients suffer from substantial psychological and financial burdens, thus adding to a significantly impaired quality of life. Traditional systemic therapies for psoriasis, such as methotrexate, cyclosporin A, retinoids or PUVA therapy, have a potential for long-term toxicity and may not always provide sufficient improvement of the disease. The development of novel therapies targeting key steps in the pathogenesis of psoriasis and psoriatic arthritis now provide new and efficient treatment options. Biological therapies for the treatment of psoriasis and/or psoriatic arthritis are defined by their mode of action and can be classified into three categories: the T-cell modulating agents (alefacept and efalizumab), the inhibitors of tumour necrosis factor-α (TNFα blockers, e.g. adalimumab, certolizumab, etanercept, golimumab and infliximab) and the inhibitors of interleukin (IL) 12 and IL-23 (e.g. ustekinumab and briakinumab). This article provides a brief overview of the currently approved biological agents in the European Union and of some newer agents, such as briakinumab, certolizumab and golimumab.
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Keywords: briakinumab; certolizumab; golimumab; psoriasis; psoriatic arthritis; ustekinumab

Abbreviations: ACR, American College of Rheumatology; DAS, Disease Activity Score; DLQI, Dermatological Life Quality Index; DMARD, disease modifying anti-rheumatic drugs; HAQ, Health Assessment Questionnaire; ICAM, intracellular adhesion molecule-1; IL, interleukin; LFA, leukocyte function antigen; MTX, methotrexate; NAPSI, Nail Psoriasis Severity Index; NSAID, non-steroidal anti-inflammatory drugs; PASI, Psoriasis Activity and Severity Index; PGA, Physician's Global Assessment; PML, progressive multifocal leukoencephalopathy; PsA, psoriatic arthritis; RCTs, randomized controlled trials; TNF-α, tumour necrosis factor-α

Introduction

Psoriasis is a common chronic inflammatory disease with a complex pathophysiology and a strong genetic background (Liu *et al.*, 2007; Nickoloff *et al.*, 2007; Valdimarsson, 2007). It affects approximately 1–3% of the general population worldwide (Schön and Boehncke, 2005; Griffiths and Barker, 2007; FitzGerald and Winchester, 2009; Nestle *et al.*, 2009; Nograles *et al.*, 2009; Pathirana *et al.*, 2009). The main type of psoriasis is chronic plaque psoriasis accounting for approximately 85–90% of all cases (Griffiths and Barker, 2007; Nestle *et al.*, 2009). Other forms of psoriasis comprise guttate psoriasis, erythrodermic, inverse, palmoplantar and localized, as well as generalized pustular psoriasis (Schön and Boehncke, 2005; Griffiths and Barker, 2007; Nestle *et al.*, 2009). Psoriatic arthritis (PsA) involves peripheral joints, the axial skeleton, sacroiliac joints, nails and entheses, and is usually associated with psoriatic skin lesions (FitzGerald and Winchester, 2009; Gladman, 2009; Nograles *et al.*, 2009; Pathirana *et al.*, 2009). The prevalence of PsA ranges from 5 to 40% among psoriatic patients lesions (FitzGerald and Winchester, 2009; Gladman, 2009; Nograles *et al.*, 2009; Pathirana *et al.*, 2009). Two large studies conducted in a German population reported a prevalence of 19 and 20.6%, respectively (Radtke *et al.*, 2009; Reich *et al.*, 2009), which seems to be a close estimate to the true prevalence of PsA in Central Europe. Recently, co-morbidities like cardiovascular disease, obesity and metabolic syndrome have been found to be associated with psoriasis, raising the possibility that psoriasis might not be only a skin disorder (Kimball *et al.*, 2008a; Menter *et al.*, 2008a; Gerdes and

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Mrowietz, 2009). Due to the chronic nature of the disease, patients suffer from substantial psychological and financial burdens resulting in a significantly impaired quality of life (Rapp *et al*., 1999).Traditional systemic therapies for psoriasis (methotrexate [MTX], cyclosporin A, retinoids or PUVA therapy) have a potential for long-term toxicity and may not always provide sufficient improvement of the disease (Pathirana *et al*., 2009; Smith *et al*., 2009a). Thus, the development of agents efficiently targeting key steps in the pathogenesis of psoriasis and PsA is clearly an important goal.

Immunopathogenesis

Psoriasis is thought to be an immune-mediated disease with a genetic basis involving a complex interrelationship between hyperplastic epidermal keratinocytes and several immune cell types including T cells, neutrophils, dendritic cells and macrophages (Ellis *et al*., 1986; Toichi *et al*., 2006; Liu *et al*., 2007; Lowes *et al*., 2007; Nickoloff *et al*., 2007; Nestle, 2008; Nestle *et al*., 2009). A variety of cytokines has also been implicated in the pathogenesis of psoriasis. Among other cytokines tumour necrosis factor-α (TNF-α) as well as interleukin 12 (IL-12) and IL-23 are well known to be crucial immunological mediators in psoriasis. Whereas IL-12 induces Th-1 differentiation and thus increases the production of TNF-α, IL-23 stimulates primarily Th-17 cells, which are characterized by the synthesis of the pro-inflammatory mediators such as IL-17 and IL-22 (Toichi *et al*., 2006; Fitch *et al*., 2007; Sabat *et al*., 2007; Torti and Feldman, 2007; Nograles *et al*., 2008; Nestle *et al*., 2009). Increased concentrations of TNF-α and IL-12/IL-23 have been found in psoriatic skin compared with non-lesional skin (Lee *et al*., 2004; Vandenbroeck *et al*., 2004; Nestle *et al*., 2009). TNF-α as well as IL-12 were also found to be elevated in the synovial fluid and tissue of patients suffering from PsA (Ritchlin *et al*., 1998; FitzGerald and Winchester, 2009). Their role in psoriasis is highlighted by the efficient and successful treatment of psoriasis by agents blocking these cytokines (Boker *et al*., 2007; Fantuzzi *et al*., 2008; Mössner *et al*., 2008; Scalon *et al*., 2009; Sobell *et al*. 2009a). In addition, polymorphisms of genes encoding the IL-23 receptor and the shared p40 subunit of IL-12 and IL-23 (interleukin 12B) have been linked to the development of psoriasis (Cargill *et al*., 2007; Smith *et al*., 2008; Elder *et al*., 2009; Hüffmaier *et al*., 2009; Nestle *et al*., 2009; Smith *et al*., 2009b). A detailed review of the immunopathogenesis of psoriasis is beyond the scope of this article but has been provided by several recent publications (Bowcock and Krueger, 2005; Hueber and McInnes, 2007; Liu *et al*., 2007; Lowes *et al*., 2007; Sabat *et al*., 2007; Nestle, 2008; FitzGerald and Winchester, 2009; Nestle *et al*., 2009; Nograles *et al*., 2009).

Assessments

To assess the severity of psoriasis and PsA at baseline and in response to treatment, a number of tools are now available, of which the Psoriasis Activity and Severity Index (PASI) is the most commonly used at present (Fredriksson and Pettersson, 1978). The PASI combines assessments of the extent of body surface involvement in four anatomical regions (head, trunk, arms and legs) and the severity of desquamation, erythema and plaque induration (thickness) in each region, yielding an overall score of 0 (no psoriasis) to 72 (severe psoriasis) (Fredriksson and Pettersson, 1978). PASI 75 is defined as a 75% reduction in PASI compared with baseline. According to the European S3 guidelines, a PASI score of >10 is defined as moderate to severe disease, necessitating systemic therapy (PUVA, UVB 311, MTX, cyclosporin A or biological agents) (Pathirana *et al*., 2009; Smith *et al*., 2009a). A further tool to assess the severity of psoriasis is the physician's global assessment (PGA). The PGA takes into account the involvement of the body surface area, induration, scaling and erythema and grades the patient's psoriasis overall, relative to baseline, as 1 (clear), 2 (excellent), 3 (good), 4 (fair), 5 (poor) or 6 (worse) (Pathirana *et al*., 2009). In trials investigating patients with PsA, the American College of Rheumatology Criteria (ACR) are most commonly used. The ACR clinical response criteria are defined as percentage reduction [20% (ACR 20), 50% (ACR 50) and 70% (ACR 70)] in tender and swollen joint counts and in three of the remaining five ACR core items (patient and physician global assessments, pain, disability and an acute phase reactant) (Kyle *et al*., 2005; Montecucco, 2006; Radtke *et al*., 2009). A further tool to measure clinical remission in psoriatic and rheumatoid arthritis patients is the Disease Activity Score (DAS) comprising the number of swollen and tender joints, the erythrocyte sedimentation rate and the general health of the patient (measured on a visual analogue scale) (Van Gestel *et al*., 1996; Montecucco, 2006; Gladman, 2009). The DAS measures 44 swollen joints, whereas the modified DAS 28 measures only 28 swollen and tender joints (Prevoo *et al*., 1995). The effect of psoriasis on the patient's quality of life is measured by the 10-item Dermatology Life Quality Index (DLQI) questionnaire. DLQI scores range from 0 (not at all) to 30 (very much) (Pathirana *et al*., 2009; Smith *et al*., 2009a).

Biological agents

Biological therapies for the treatment of psoriasis and/or PsA are defined by their mode of action and are classified into three categories, the T-cell modulating agents (alefacept and efalizumab), the inhibitors of tumour necrosis factor-α (TNFα blockers, e.g. adalimumab, certolizumab, etanercept, golimumab, and infliximab), and the inhibitors of IL-12 and IL-23 (ustekinumab and briakinumab).

T-cell modulators

In 2003, alefacept and efalizumab were the first biological agents to be approved by the Food and Drug Administration (FDA) for the treatment of psoriasis (Menter *et al*., 2008a; Sugiyama *et al*., 2008; Pathirana *et al*., 2009). In the European Union, only efalizumab was approved for the treatment of moderate to severe plaque psoriasis (Pathirana *et al*., 2009). In 2009, efalizumab was withdrawn from the market in Europe and the United States [FDA, 2009; European Medicines Agency (EMEA), 2009].

Alefacept

Alefacept, a recombinant dimeric fusion protein, is made up of the terminal portion of leukocyte function antigen-3 (LFA-3). It binds to extracellular human CD2 and the Fc portion of human immunoglobulin IgG_1 (Sugiyama *et al.*, 2008). Alefacept blocks signalling between LFA-3 on antigen presenting cells and the CD2 molecule on T cells (primarily CD45RO+). Subsequently, the activation and proliferation of CD45RO+ T cells, which account for approximately 75% of T lymphocytes in psoriatic lesions, are inhibited. Furthermore, alefacept decreases the number of pathogenic T cells by binding CD2 on CD45RO+ T-lymphocytes to the FcγIII receptor on natural killer cells, resulting in granzyme-mediated apoptosis of T cells (Gordon *et al.*, 2003; Ortonne *et al.*, 2003; Sugiyama *et al.*, 2008; Sobell *et al.*, 2009b). Using a dosage of 15 mg alefacept administered intramuscularly QW, PASI 75 scores at week 12 were found to range between 21 and 35% (Ellis and Krueger, 2001; Gordon *et al.*, 2003; Ortonne *et al.*, 2003; Mease *et al.*, 2006; Menter *et al.*, 2008a; Sugiyama *et al.*, 2008; Pathirana *et al.*, 2009). Recently, patients receiving alefacept in combination with MTX were shown to improve significantly in ACR 20 at week 24 compared with patients treated with MTX and placebo alone (54% vs. 23%; $P < 0.001$) (Mease *et al.*, 2006).

Efalizumab

Efalizumab is a recombinant humanized IgG_1 monoclonal antibody binding to the human CD11a subunit in leukocyte function antigen-1 (LFA-1) and therefore blocks the binding of LFA-1 to intracellular adhesion molecule-1 (ICAM-1). The prevention of signal transduction to LFA-1 causes loss of activation, adhesion and migration of T-cells. Efalizumab also decreases epidermal hyperplasia, ICAM-1 and keratin-16 expression (Boehncke, 2007; Selenko-Gebauer *et al.*, 2007; Schön, 2008; Sobell *et al.*, 2009b). PASI 75 scores observed in phase III studies ranged from 22 to 39% at week 12 (Boehncke, 2007; Boker *et al.*, 2007; Selenko-Gebauer *et al.*, 2007; Menter *et al.*, 2008a; Schön, 2008; Sobell *et al.*, 2009b). A phase II study in PsA patients, however, did not reveal significant improvement in ACR 20 responses (Papp *et al.*, 2007). Efalizumab was well tolerated by most patients. The most common adverse events comprised flu-like reactions, upper respiratory infections and arthralgias (Boehncke, 2007; Papp *et al.*, 2007; Selenko-Gebauer *et al.*, 2007; Schön, 2008; Sobell *et al.*, 2009b). As three patients with long-term efalizumab treatment (3 years of treatment) developed progressive multifocal leukoencephalopathy (PML), efalizumab was voluntarily withdrawn from the market by the manufacturing company in 2009 because the risk-benefit ratio for treating psoriasis was no longer considered to be favourable (Carson *et al.*, 2009; EMEA, 2009; FDA, 2009; Korman *et al.*, 2009).

TNF-α inhibitors

As the TNF-α inhibitors adalimumab, etanercept and infliximab have been approved by the FDA and EMEA for psoriasis and PsA, and have been reviewed quite extensively in the past, this article will focus on the new TNF-α blockers such as golimumab, which has been recently approved by the EMEA (September 30, 2009) for the treatment of PsA and certolizumab (Menter *et al.*, 2008a; Mössner *et al.*, 2008; Pathirana *et al.*, 2009). Clinical outcome for primary endpoints (e.g. PASI and ACR) in randomized controlled trials using adalimumab, etanercept and infliximab is given in Tables 1 and 2 (Mease *et al.*, 2000; 2004; 2005; 2009; Chaudhari *et al.*, 2001; Gottlieb *et al.*, 2003; 2004; Leonardi *et al.*, 2003; Antoni *et al.*, 2005; Papp *et al.*, 2005; Reich *et al.*, 2005; Gordon *et al.*, 2006; Tyring *et al.*, 2006; Woolacott *et al.*, 2006a,b; Genovese *et al.*, 2007; Gladman *et al.*, 2007; Kavanaugh *et al.*, 2007; Menter *et al.*, 2007; 2008b; Saurat *et al.*, 2008; Traczewski and Rudnicka, 2008). Up to now, treatment with antibodies directed towards TNF-α has proven to be effective and relatively safe in patients suffering from psoriasis and PsA (Lima *et al.*, 2009a). Safety data for TNF-α inhibitors and ustekinumab are shown in Table 3 (Pathirana *et al.*, 2009; Smith *et al.*, 2009a).

Golimumab (formerly CNTO148)

Golimumab is a human immunoglobulin $G1_K$ monoclonal antibody binding with high affinity and specificity to both soluble and transmembrane forms of TNF-α, thereby neutralizing their bioactivity by blocking the interaction with TNF-α receptors (Kavanaugh *et al.*, 2009a; Xu *et al.*, 2009).

Pharmacokinetics

In a study comprising 2029 serum golimumab concentrations from 337 patients participating in the GO-REVEAL trial population, the pharmacokinetics of subcutaneously administered golimumab (50 or 100 mg every 4 weeks) were analysed (Xu *et al.*, 2009). The following golimumab pharmacokinetic parameters (for patients of standard weight of 70 kg) were found: apparent clearance = 1.38 ± 0.04 L·per day, apparent volume of distribution = 24.9 ± 1.04 L and absorption rate constant = 0.908 ± 0.121 per day. Between-subject variability was found to be 37.6% in apparent clearance and 37.9% in apparent volume of distribution. Significant covariants on apparent clearance were identified as body weight, antibody to golimumab status, baseline C-reactive protein level and smoking habits. However, only body weight was found to be a significant covariant on apparent volume of distribution. The observed variability in systemic exposure to golimumab in PsA patients might be at least partly explained by these covariants. In addition, golimumab concentrations in patients (50 mg golimumab every 4 weeks) not receiving MTX were 30% lower as compared with patients receiving MTX (Xu *et al.*, 2009). However, no significant difference in golimumab concentrations between patients receiving golimumab 100 mg every 4 weeks and once weekly MTX and those in patients not receiving MTX was observed. So far, no explanation for the different effects of MTX on the serum golimumab concentrations has been provided (Xu *et al.*, 2009).

Table 1 Efficacy of TNF-α blockers and IL-12/IL-23 antagonists in the therapy of psoriasis vulgaris (randomized controlled trials)

Agent	*Reference*	*Trial*	*Treatment (number of patients)*	*Results (%)*
Adalimumab	Gordon *et al.*, 2006	12-week RDBPC OLE until week 60	A 40 mg weekly (50) A 40 mg eow (46) Placebo (52)	PASI 75 at week 12: 80 PASI 75 at week 12: 53 PASI 75 at week 12: 4
Adalimumab (REVEAL)	Menter *et al.*, 2008b	16-week RDBPC OLE until week 52	A 40 mg eow (814) Placebo (398)	PASI 75 at week 16: 71 PASI 75 at week 16: 7
Adalimumab (CHAMPION)	Saurat *et al.*, 2008	16-week RDBPC	A 40 mg eow (108) MTX (110) Placebo (53)	PASI 75 at week 16: 80 PASI 75 at week 16: 36 PASI 75 at week 16: 19
Briakinumab	Kimball *et al.*, 2008b	12-week RDBPC	B 200 mg × 1 (30) B 100 mg eow (3) B 200 mg × 4 (30) B 200 mg eow (30) B 200 mg weekly (30) Placebo (30)	PASI 75 at week 12: 63 PASI 75 at week 12: 93 PASI 75 at week 12: 90 PASI 75 at week 12: 93 PASI 75 at week 12: 90 PASI 75 at week 12: 1
Etanercept	Gottlieb *et al.*, 2003	12-week RDBPC	E 25 mg twice weekly (57) Placebo (55)	PASI 75 at week 12: 30 PASI 75 at week 12: 2
Etanercept CONSORT	Papp *et al.*, 2005	RDBPC	E 25 mg twice weekly (196) E 50 mg twice weekly (194) Placebo (193)	PASI 75 at week 12: 34 PASI 75 at week 12: 49 PASI 75 at week 12: 3
Etanercept	Leonardi *et al.*, 2003	RDBPC	E 25 mg weekly (160) E 25 mg twice weekly (162) E 50 mg twice weekly (164) Placebo (166)	PASI 75 at week 12: 14 PASI 75 at week 12: 34 PASI 75 at week 12: 49 PASI 75 at week 12: 4
Etanercept	Tyring *et al.*, 2006	12-week RDBPC	E 50 mg twice weekly (311) Placebo (307)	PASI 75 at week 12: 47 PASI 75 at week 12: 5
Golimumab GO-REVEAL	Kavanaugh *et al.*, 2009a	24-week RDBPC	G 50 mg q4 wks (146) G 100 mg q4 wks (146) Placebo (113)	PASI 75 at week 14: 40 PASI 75 at week 14: 58 PASI 75 at week 14: 3
Infliximab SPIRIT	Gottlieb *et al.*, 2004	RDBPC	Infliximab 3 mg·kg^{-1} (99) Infliximab 5 mg·kg^{-1} (99) Placebo (51)	PASI 75 at week 10: 72 PASI 75 at week 10: 88 PASI 75 at week 10: 6
Infliximab EXPRESS I	Reich *et al.*, 2005	RDBPC	Infliximab 5 mg·kg^{-1} (301) Placebo (77)	PASI 75 at week 10: 80 PASI 75 at week 10: 3
Infliximab	Chaudhari *et al.*, 2001	RDBPC	Infliximab 5 mg·kg^{-1} (11) Infliximab 10 mg·kg^{-1} (11) Placebo (11)	PASI 75 at week 10: 82 PASI 75 at week 10: 73 PASI 75 at week 10: 18
Infliximab EXPRESS II	Menter *et al.*, 2007	RDBPC	Infliximab 3 mg·kg^{-1} (311) Infliximab 5 mg·kg^{-1} (314) Placebo (208)	PASI 75 at week 10: 70 PASI 75 at week 10: 76 PASI 75 at week 10: 2
Ustekinumab PHOENIX 1	Leonardi *et al.*, 2008	RDBPC	Ustekin 45 mg (255) Ustekin 90 mg (256) Placebo (255)	PASI 75 at week 12: 67.1 PASI 75 at week 12: 66.4 PASI 75 at week 12: 3.1
Ustekinumab PHOENIX 2	Papp *et al.*, 2008	RDBPC	Ustekin 45 mg (409) Ustekin 90 mg (411) Placebo (410)	PASI 75 at week 12: 66.7 PASI 75 at week 12: 75.7 PASI 75 at week 12: 3.7
Ustekinumab ACCEPT	Griffiths *et al.*, 2008	RDBPC	Ustekin 45 mg (209) Ustekin 90 mg (347) E 2 × 50 mg (347)	PASI 75 at week 12: 67.5 PASI 75 at week 12: 73.8 PASI 75 at week 12: 56.8

A, adalimumab; B, briakinumab; E, etanercept; eow, every other week; G, golimumab; OLE, open level extension; q4 wks, every 4 weeks; RDBPC, randomized double-blind placebo controlled trial; Ustekin, ustekinumab.

Phase III studies

A randomized, double-blind, placebo-controlled phase III multicenter study (GO-REVEAL) was conducted to evaluate the safety and efficacy of golimumab administered subcutaneously every 4 weeks from week 0 to 20 in patients suffering from PsA (Kavanaugh *et al.*, 2009a). Four hundred five patients were enrolled at 58 sites. Eligible patients were adults with active PsA for at least 6 months despite therapy with disease modifying anti-rheumatic drugs or non-steroidal anti-inflammatory drugs (NSAIDs). Active PsA was defined as at least three swollen joints and three tender joints as well as active plaque psoriasis with a qualifying lesion of at least 2 cm in diameter. Concomitant MTX (approximately 50% of patients in each group received a median dose of 15 mg·week^{-1}), NSAIDs and corticosteroids (prednisone equivalent ≤ 10 mg·per day) were permitted at stable doses. Patients previously treated with anti-TNF-α agents, rituximab, natalizumab or cytotoxic agents were excluded from the trial.

A significant reduction in PASI 75 among patients receiving golimumab 50 or 100 mg at week 14 (40 and 58%) was observed when compared with patients receiving placebo (3%). PASI 75 scores in patients with golimumab (50 and 100 mg) further improved at week 24 in both golimumab groups (56 and 66%), whereas only 1% of patients in the placebo group reached a PASI 75 (Kavanaugh *et al.*, 2009a). Data presented (104 weeks) at the 2009 Annual Meeting of the European Rheumatologists in Copenhagen (at the time only available as an abstract) revealed PASI 75 in 68.8% of

Table 2 Efficacy of TNF-α inhibitors in the therapy of psoriatic arthritis (randomized controlled trials)

Agent	*Reference*	*Trial*	*Treatment (number of patients)*	*Results (%)*
Adalimumab (ADEPT)	Mease *et al.*, 2005	24-week RDBPC	A 40 mg eow (151)	ACR 20 at week 12: 58
	Gladman *et al.*, 2007	OLE	Placebo (162)	ACR 20 at week 12: 14
	Mease *et al.*, 2009	OLE week 48	OLE A (281)	ACR 20 at week 48: 58.7
		OLE week 104		ACR 20 at week 104: 57.3
Adalimumab	Genovese *et al.*, 2007	12-week RDBPC	A 40 mg eow (51)	ACR 20 at week 12: 39
		OLE until week 24	Placebo (49)	ACR 20 at week 12: 16
Etanercept	Mease *et al.*, 2000	12-week RDBPC	E 25 mg twice weekly (30)	ACR 20 at week 12: 73
			Placebo (30)	ACR 20 at week 12: 13
Etanercept	Mease *et al.*, 2004	24-week RDBPC	E 25 mg twice weekly (101)	ACR 20 at week 12: 59
		OLE until week 48	Placebo (104)	ACR 20 at week 12: 15
Golimumab GO-REVEAL	Kavanaugh *et al.*, 2009a	24-week RDBPC	G 50 mg q4wks (146)	ACR 20 at week 14: 51
			G 100 mg q4wks (146)	ACR 20 at week 14: 45
			Placebo (113)	ACR 20 at week 14: 9
Infliximab IMPACT	Antoni *et al.*, 2005	16-week RDBPC	Infliximab 5 mg·kg^{-1} (52)	ACR 20 at week 16: 65
		OLE week 50	Placebo (52)	ACR 20 at week 16: 10
Infliximab IMPACT II	Kavanaugh *et al.*, 2007	24-week RDBPC	Infliximab 5 mg·kg^{-1} (100)	ACR 20 at week 24: 54
		OLE 52 weeks	Placebo (100)	ACR 20 at week 24: 16

A, adalimumab; E, etanercept; eow, every other week; G, golimumab; OLE, open level extension; q4wks, every 4 weeks; RDBPC, randomized double-blind placebo controlled trial.

Table 3 Overview of reported important side effects of TNF-α inhibitors and ustekinumab (Pathirana *et al.*, 2009; Smith *et al.*, 2009a)

	Adalimumab	*Etanercept*	*Infliximab*	*Ustekinumab*
Common side effects	URTI	URTI	URTI	URTI
	Injection site reactions	Injection site reactions	Acute infusion reaction (fever, chills, nausea)	
	Headache		Headache	Headache
		Pruritus	Pruritus	
			Urticaria	
			Elevated transaminases	
Uncommon but severe side effects	Severe infections	Severe infections	Severe infections	Severe infections
	Opportunistic infections	Opportunistic infections	Opportunistic infections	
	Reactivation of latent tuberculosis or progression of recently acquired tuberculosis	Reactivation of latent tuberculosis or progression of recently acquired tuberculosis	Reactivation of latent tuberculosis or progression of recently acquired tuberculosis	Possible reactivation of latent tuberculosis or progression of recently acquired tuberculosis
	New onset or exacerbation of CNS demyelinating disorders (e.g. multiple sclerosis)	New onset or exacerbation of CNS demyelinating disorders (e.g. multiple sclerosis)	New onset or exacerbation of CNS demyelinating disorders (e.g. multiple sclerosis)	
	Possible increased risk of malignancy (in particular lymphoma)	Possible increased risk of malignancy (in particular lymphoma)	Possible increased risk of malignancy (in particular lymphoma)	Possible increased risk of malignancy
	Drug-induced lupus	Drug-induced lupus	Drug-induced lupus	
	Exacerbation of congestive heart failure	Exacerbation of congestive heart failure	Exacerbation of congestive heart failure	Mycordial infarction/Stroke
	Vasculitis	Vasculitis	Vasculitis	
		Aplastic anaemia	Pancytopenia	

URTI, upper respiratory tract infections.

patients in the golimumab 50-mg group and 76% in the golimumab 100-mg group (Kavanaugh *et al.*, 2009b). Gladman *et al.* (2008) also assessed the Nail Psoriasis Severity Index (NAPSI) at baseline and week 24. Significant improvement of median NAPSI scores was observed in both golimumab groups (33% and 54%) versus 0% in the placebo group.

Golimumab significantly improved signs and symptoms of PsA compared with patients treated with placebo (Kavanaugh *et al.*, 2009a). An ACR 20 response at week 14 could be achieved in 51% of patients treated with golimumab 50 mg and in 45% of patients receiving golimumab 100 mg versus only 9% in the placebo group ($P < 0.001$ for both comparisons). At week 24, an ACR 20 response was observed in 52% in the golimumab 50-mg group and in 61% in the golimumab 100-mg group versus 12% in the placebo group ($P < 0.001$ for both comparisons). ACR 50 and 70 responses were also

significantly higher in both golimumab groups than in the placebo group. At week 104, 91.4% of patients in the 50-mg group and 73.1% in the 100-mg group achieved an ACR 20 (Kavanaugh *et al*., 2009b). A good or moderate DAS 28 response was significantly ($P < 0.001$ for all comparisons) more often achieved in the golimumab 50 and 100-mg recipients than in the placebo group at week 14 (66 and 67% vs. 24%) and at week 24 (64 and 78% vs. 24%) (Kavanaugh *et al*., 2009a). Assessment of physical function and health-related quality of life were measured by the Health Assessment Questionnaire (HAQ) and Short Form 36 Health Survey (SF-36) and significantly improved in both golimumab groups compared with the placebo group ($P < 0.001$ for HAQ and SF-36 at all comparisons at week 24).Thus, in this study golimumab improved significantly the clinical signs and symptoms of PsA as well as the physical function and quality of life (Kavanaugh *et al*., 2009a).

Safety

Kavanaugh *et al*. (2009b) reported that 8.6% of patients treated with golimumab experienced a serious adverse event up to week 104. Serious infectious adverse events comprised sepsis/cholecystitis and abscess formation. The following malignancies were noted through week 104: one basal cell carcinoma, one colon cancer and one small lung cell carcinoma in the golimumab 50-mg group. In the golimumab 100-mg group, three basal cell carcinomas, one prostate cancer and one small lung cancer occurred. As for adverse events, infections of the upper respiratory tract and nasopharyngitis were most frequently reported. Infections were more common in the golimumab 100-mg group (41%) compared with the golimumab 50-mg group (33%), otherwise no differences between the two groups were noted. Injection site reactions occurred in 8.9% of golimumab-treated patients and with 0.7% of all golimumab injections through week 104 (Kavanaugh *et al*., 2009b).

Certolizumab pegol (CDP870)

Certolizumab pegol, a pegylated Fab-9 fragment of a humanized anti TNF-α antibody, has been approved for the treatment of patients with moderate to severe Crohn's disease (Bourne *et al*., 2008) and it has also been investigated in patients with rheumatoid arthritis (Barnes and Moots, 2007). It binds to TNF-α, thus blocking the interaction with cell surface receptors. Whereas adalimumab, etanercept and infliximab contain an IgG1 Fc region, which can induce antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), certolizumab lacks this Fc region. It is therefore not capable of inducing ADCC and CDC (Bourne *et al*., 2008).

Pharmacokinetics

So far, no data are available concerning the pharmacokinetics of certolizumab in psoriatic patients. Pharmacokinetic analysis in the CDP870-039 trial showed a bioavailability of 85% (EMEA, 2008). Peak plasma concentrations were attained between 54 and 171 h after subcutaneous injection. The mean serum concentration (C_{max}) after the subcutaneous administration of 400-mg certolizumab ranged from 46.3 ± 13.1 to 49.5 ± 8.2 $\mu g \cdot mL^{-1}$. An increase of serum concentration (C_{max}) and area under the curve (AUC) was observed with higher doses in a dose-proportional manner. The half-life of certolizumab was found to be approximately 14 days (EMEA, 2008).

Phase II studies

Certolizumab pegol has been investigated in patients with moderate to severe plaque psoriasis. In a phase II trial, patients were randomized to receive certolizumab pegol 200 mg, 400 mg or placebo subcutaneously every 2 weeks up to week 12. At week 12, significantly more patients receiving certolizumab pegol 200 or 400 mg achieved PASI 75 than in the placebo group (74.6 and 82.8% vs. 6.8%) (Ortonne *et al*., 2007). The most frequently reported adverse events comprised headache, nasopharyngitis and pruritus. The frequency of adverse events was similar across all three groups. However, serious adverse events were more common in the 400-mg group (7.0%) than in the 200-mg group (3.3%) and in the placebo-group (1.7%) (Ortonne *et al*., 2007). According to the data from the phase II study, PASI 75 results and side effects were comparable with those observed in patients treated with the approved TNF-α blockers adalimumab and infliximab. So far, no phase III studies or studies in patients with PsA have been conducted (http://clinicaltrials.gov, last accessed on 15 December 2009).

IL-12/IL-23 antagonists

Briakinumab and ustekinumab are both IL-12/IL-23 antagonists. Whereas briakinumab is currently under investigation for the treatment of psoriasis in several phase III studies, ustekinumab was recently approved for the treatment of chronic plaque psoriasis by the EMEA.

Briakinumab (formerly ABT874)

Briakinumab is a recombinant fully human, IgG1 monoclonal antibody targeting the shared p40 subunit of IL-12 and IL-23 (Kimball *et al*., 2008b) It binds to soluble forms of IL-12 and IL-23, leading to a decreased secretion of IL-12, IL-6, interferon-γ (IFN-γ) and TNF-α, as shown in patients suffering from Crohn's disease (Mannon *et al*., 2004; Ding *et al*., 2008).

Pharmacokinetics

In a phase I trial conducted among 64 healthy volunteers, the pharmacokinetics of briakinumab (0.1–5.0 $mg \cdot kg^{-1}$ subcutaneously or intravenously) were evaluated. A linear relationship between the maximum serum concentration (C_{max}) and AUC (concentration-time) was found with increasing doses. The terminal phase half-life time was approximately 9 days. No dose dependency was found for the volume distribution at steady state and the clearance of the drug. Subcutaneous and

intramuscular application achieved an absolute bioavailability of 42 and 63% respectively (Ding *et al*., 2008; Lima *et al*., 2009b; Paulsen *et al*., 2009).

Phase II studies

Kimball *et al*. (2008b) conducted a dose finding study with briakinumab in patients with moderate to severe plaque psoriasis. Patients were randomized in groups of 30 to receive either only one dose of briakinumab 200 mg at week 0, 100 mg briakinumab every other week for 12 weeks, 200 mg weekly for 4 weeks, 200 mg every other week for 12 weeks and 200 mg every week for 12 weeks, or placebo respectively (Kimball *et al*., 2008b). PASI 75 was significantly more often reached in patients in all five briakinumab treatment groups (63, 93, 90, 93, and 90% respectively) compared with the placebo group (3%, $P < 0.001$). Statistically significant improvement to briakinumab therapy was rapid and could be noted in the briakinumab groups as early as at week 1. During the 12-week duration, improvement could be sustained in briakinumab-treated patients even for patients in the briakinumab 200 mg × 1 and 200 mg × 4 dosage groups.

Adverse events

Injection site reactions were the leading adverse event in the trial conducted by Kimball *et al*. (2008b). Although no serious infectious adverse events were reported in this trial, other common side effects comprised nasopharyngitis and upper respiratory infections. In addition, non-infectious serious adverse events reported in this study included costal chondritis (one patient in the briakinumab 200 mg × 1 group). Significantly more patients in the briakinumab groups (36%) experienced adverse events compared with the placebo group (10%).

Ustekinumab (formerly CNTO1275)

Ustekinumab is a human monoclonal antibody binding with high affinity to the p40 subunit of IL 12 and IL 23 and therefore inhibiting the two cytokines from binding to their associated receptor (IL-12Rβ1) expressed on a variety of cells. In a phase I study, patients with sustained PASI improvement (defined as 70% PASI improvement) at weeks 8, 12 and 16 showed significant decreases in mRNA expression of cytokines IL-8, IL-18 and IFN-γ as early as week 1 ($P < 0.05$), whereas, in patients without PASI improvement, no significant reduction of cytokine mRNA expression was noted (Wittig, 2007).

Pharmacokinetics

In both phase I studies, the pharmacokinetics of ustekinumab were assessed (Kaufmann *et al*., 2004; Gottlieb *et al*., 2007; Wittig, 2007). They showed that, after a single subcutaneous injection, ustekinumab was slowly absorbed into the systemic circulation (mean T_{max} approximately 12 days) and was afterwards slowly eliminated from the circulation (mean $t_{1/2}$ approximately 20 days) (Gottlieb *et al*., 2007; Wittig, 2007). The terminal half-life ($t_{1/2}$) was dose dependent and was found to range from 14.9 ± 4.6 days (0.27 mg·kg^{-1} dose group) to 28.6 ± 9.3 days (2.7 mg·kg^{-1} dose group) (Gottlieb *et al*., 2007). Similar results were also observed for $t_{1/2}$ by Kaufman *et al*. (2004), ranging from 18.5 ± 3.6 in the 0.3-mg group to 25.9 ± 3.7 in the 1.0-mg group. Interestingly in the clinical trials, the effects of ustekinumab were sustained much longer than expected from the half-life of 20 days. The reason for this phenomenon has still to be elucidated. An increase of serum concentration (C_{max}) and AUC was observed with higher dosages (Kaufmann *et al*., 2004; Gottlieb *et al*., 2007).

Phase I studies

Two phase 1 studies have been published in 2004 and 2007 (Kaufmann *et al*., 2004; Gottlieb *et al*., 2007). In the clinical trial conducted by Kaufman, 18 patients with moderate to severe psoriasis (at least 3% of body surface area involvement) were enrolled in four dose groups: 0.1, 0.3, 1.0 and 5.0 mg per kg to assess the clinical response (PASI) and the safety of a single intravenous administration of ustekinumab (Kaufmann *et al*., 2004). At week 12, PASI 75 was reached in 25, 50, 60 and 100% of patients respectively. In patients responding to ustekinumab treatment, the expression of pro-inflammatory cytokines IFN-γ, IL-8, IFN-γ-inducible protein, CCR2 (MCP-1), TNF-α, IL-12p40 and IL-23p19 subunits was decreased, compared with baseline levels (Toichi *et al*., 2006; Reddy *et al*., 2007).

In a second double-blind, placebo-controlled study, patients were randomized to receive either a single subcutaneous injection of 0.27, 0.675, 1.35 or 2.7 mg·kg^{-1} ustekinumab or placebo (Gottlieb *et al*., 2007). Again, patients treated with ustekinumab showed a dose-dependent improvement of their psoriasis. PASI 75 was achieved in 60% of the 0.27 mg·kg^{-1} group, 100% in the 0.675 mg·kg^{-1} group, 50% in the 1.35 mg·kg^{-1} group and 100% in the 2.7 mg·kg^{-1} group, but in none of the patients receiving placebo during the whole study period.

Phase II studies

Krueger *et al*. (2007) evaluated in a double-blind, placebo-controlled trial, four subcutaneous dosing regimens of ustekinumab in patients with moderate to severe plaque psoriasis. Three hundred twenty patients were randomized to receive one of the following treatment regimens: one 45-mg dose, one 90-mg dose, four weekly 45-mg doses and four weekly 90-mg doses of ustekinumab or placebo. The primary endpoint of the study was a 75% improvement in the PASI at week 12. PASI 75 was achieved in 52% of patients receiving ustekinumab 45 mg, in 59% receiving ustekinumab 90 mg, in 67% receiving four weekly 45-mg doses and in 81% of patients receiving four weekly 90-mg doses, whereas only 2% of patients in the placebo group achieved a PASI 75.

Gottlieb *et al*. (2009) conducted a placebo-controlled double blind randomized crossover study to evaluate the efficacy of ustekinumab in 146 patients suffering from PsA. Patients were either randomized to receive ustekinumab 90 or 63 mg every week for 4 weeks (weeks 0–3) followed by placebo at weeks 12 and 16 (76 patients, group 1) or placebo (weeks 0–3) and ustekinumab (63 mg) at weeks 12 and 16 (70

patients, group 2). ACR 20 at week 12 (taken as the primary endpoint of the study) was achieved by 42% of patients in group 1 and by 14% in group 2 ($P = 0.0002$). Significantly more patients in group 1 achieved PASI 75 compared with group 2 in week 12 (52% vs. 5%, $P < 0.0001$). However, one should note that the dosages of ustekinumab used in the study were higher (90 and 63 mg, respectively) than those recommended for patients of normal weight (45 mg) with psoriasis, as shown in the prescription information for ustekinumab (Product Monograph, 2008).

Phase III studies

Two large double-blind, placebo-controlled phase III studies (Phoenix 1 and Phoenix 2) in patients with moderate to severe psoriasis were performed parallel in the United States and Europe respectively. Primary outcome in both studies was PASI 75 at week 12 (Leonardi *et al*., 2008; Papp *et al*., 2008). Seven hundred sixty-six patients participating in the Phoenix 1 trial were randomly assigned to receive either ustekinumab 45 mg or 90 mg at weeks 0 and 4 and afterwards every 12 weeks or placebo at weeks 0 and 4 and to cross over at week 12 to ustekinumab (Leonardi *et al*., 2008). Furthermore, patients initially receiving ustekinumab and reaching a PASI 75 at weeks 28 and 40 were re-randomized at week 40 to either continue therapy with ustekinumab or to withdrawal of the study drug until loss of response. Significantly more patients in both ustekinumab groups (45 and 90 mg) received a PASI 75 at week 12 compared with the placebo group. Patients receiving maintenance therapy up to week 76 significantly better sustained PASI 75 than patients randomized to the drug withdrawal group ($P < 0.0001$). The design of the Phoenix 2 study closely resembles that of the Phoenix 1 trial (Papp *et al*., 2008). Of the 1230 patients, 409 patients were randomized to receive ustekinumab 45 mg, 411 to receive ustekinumab 90 mg and 410 to receive placebo at weeks 0 and 4. The efficacy analysis at week 12 revealed the following results for the three groups. The primary endpoint was achieved in 66.7% of the ustekinumab 45-mg group, 75.7% of the ustekinumab 90 mg and 3.7% of the placebo group ($P < 0.0001$ for both ustekinumab 45 and 90 mg vs. placebo).

Quality of life was significantly improved in the patients treated with ustekinumab compared with the placebo groups ($P < 0.0001$) in both trials (Phoenix 1 and Phoenix 2). Patients randomized to maintenance therapy in the Phoenix 1 study were able to sustain improved DLQI scores until the end of the study, whereas in patients withdrawn from the study drug, the DLQI deteriorated again (Leonardi *et al*., 2008; Papp *et al*., 2008).

In a randomized active-controlled, parallel three-arm trial (ACCEPT trial), ustekinumab (45 and 90 mg, respectively) was compared versus the TNF-α blocker etanercept (50 mg twice weekly) (Griffiths *et al*., 2008). The primary endpoint of the study was PASI 75 at week 12. Nine hundred three patients were randomized in three treatment-arms as follows: 347 patients received etanercept 50 mg subcutaneously twice weekly, 209 patients received ustekinumab 45 mg subcutaneously at weeks 0 and 4, and 347 patients received ustekinumab 90 mg subcutaneously at weeks 0 and 4. PASI 75 at week 12 was achieved by 56.8% of patients in the etanercept group, by 67.5% in the ustekinumab 45-mg group and 73.8% in the ustekinumab 90-mg group. A greater proportion of patients receiving ustekinumab (45 or 90 mg) achieved PASI 75 when compared with the etanercept group ($P = 0.012$ for ustekinumab 45 mg, $P < 0.001$ for ustekinumab 90 mg). Interestingly, PASI 75 values at week 12 in patients receiving etanercept were better than those published in previous studies (Leonardi *et al*., 2003; Papp *et al*., 2005).

Safety

In the phase I studies, no serious adverse events were reported (Kaufmann *et al*., 2004; Gottlieb *et al*., 2007). Adverse events observed in these trials included headaches, abdominal pain and common cold symptoms. Adverse events were comparable in the phase II studies between ustekinumab and placebo groups (79% vs. 72%) (Krueger *et al*., 2007). Serious adverse events in patients treated with ustekinumab were infections (two patients), myocardial infarctions (two patients), a cerebrovascular accident (one patient), non-melanoma skin cancer (two patients) and prostate cancer (one patient). In the placebo group, one patient had a basal cell carcinoma and one patient experienced aggravation of his psoriasis requiring hospitalization. In the PsA trial conducted by Gottlieb, the following serious adverse events were reported in the ustekinumab groups: syncope (one patient), respiratory tract infection (one patient), haemorrhage (one patient), stroke (one patient), congestive heart failure/myocardial infarction/hypertension (one patient), chest pain (one patient), gastric ulcer haemorrhage/abdominal pain/back pain (one patient) and basal cell carcinoma (one patient) respectively (Gottlieb *et al*., 2009). Two serious infections occurred during the placebo-controlled phase of the two large phase III trials: one case of cellulitis and one case of herpes zoster (both in the ustekinumab 90-mg group) (Leonardi *et al*., 2008; Papp *et al*., 2008). During the placebo-controlled phase of the Phoenix 2 study, a squamous cell carcinoma in a patient in the placebo group and a basal cell carcinoma in a patient in the ustekinumab 90-mg group were observed (Papp *et al*., 2008). Comparing patients on maintenance therapy with patients randomized to the withdrawal group in Phoenix 1 study did not reveal an increased infection rate between the two groups (Leonardi *et al*., 2008). However, as Th1 and Th17 blockade by ustekinumab might impair cell-mediated immunity, normal keratinocyte host immunity and defence against malignancies, close monitoring in patients on long-term treatment with ustekinumab seems to be appropriate (O'Neill and Kalb, 2009). In the ACCEPT trial, serious adverse events have been observed in 1.2% of patients in the etanercept group, 1.9% in the ustekinumab 45-mg group and 1.2% of patients in the ustekinumab 90 mg group respectively. These included four patients in each treatment group: etanercept group: abdominal pain, bacterial meningitis, nephrolithiasis, rotator cuff syndrome; 45-mg ustekinumab group: alcoholic pancreatitis, chest pain/hypertension, psychotic disorder, breast cancer; ustekinumab 90-mg group: urosepsis/renal failure, uveitis, appendicitis and gastroenteritis from food poisoning (Griffiths *et al*., 2008).

Conclusion

So far, considering published data from the clinical trials, the new biological agents have been shown to be efficient treatment options for patients suffering from psoriasis and PsA. Furthermore, they seem to have proven an acceptable risk-benefit ratio. As psoriasis is considered a life-long disease and no causal therapy for the disease is yet available, the need for safe and efficacious long-term treatments is of major importance. Taking into account the possibility that uncommon events or events occurring during long-term exposure to these drugs might emerge in the future (e.g. the development of PML in long-term patients treated with efalizumab), vigilant and careful post-marketing surveillance in patients treated with biological agents is strongly recommended.

Conflict of interest

There are no funding sources to disclose for this work. The author has been an investigator and speaker for Abbott, Centocor, Janssen-Cilag, Merck-Serono, Schering-Plough and Wyeth.

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