Psoriasis is a severe disease that is highly burdensome for patients. Patients with psoriasis tend to perceive their disease to be more severe than their dermatologists do, and so may not receive the level of treatment that they require. Systemic therapy is under-used, and there are concerns about cumulative toxicity with conventional systemic agents. There is growing evidence that biological therapies may be able to provide the safe and effective long-term maintenance therapies that patients need. The challenges of optimising psoriasis management were discussed at a satellite symposium at the Paris EADV Congress. Also at the Paris meeting, new results from the REVEAL study of adalimumab in psoriasis were presented.

Psoriasis is no longer seen as simply a skin disease, but is now recognised as a systemic inflammatory disease with chronically elevated levels of proinflammatory mediators. It is associated with metabolic syndrome \(^1\) and increased risk of coronary artery disease, heart attack and stroke compared with individuals who do not have psoriasis.

Managing psoriasis is complex and should encompass all aspects of the disease, not just the skin symptoms. It is important that therapy should be individualised for each patient, said Wolfram Sterry (Humboldt University, Berlin, Germany). Patients need to be actively involved in decision-making and in the setting of treatment goals. All relevant aspects of the disease should be reassessed regularly to ensure optimum management. Every patient with moderate-to-severe psoriasis should receive systemic therapy, Prof. Sterry said, yet in reality fewer than half are treated systemically.

A set of recommendations for minimum treatment goals in patients with moderate-to-severe psoriasis was formulated by Reich and Mrowietz in 2007 (Table 1). Prof. Sterry said that personally he would not be satisfied with a 50% improvement in skin lesions (PASI 50). “I would expect in my experience at least 75% improvement,” he observed \(^2\).

When selecting a biological treatment agent for psoriasis, it is important to consider which drug is best at treating the particular aspect of the disease that is most bothersome for the patient, Prof. Sterry continued. To avoid disappointment patients should be told how long their proposed treatment will take to work; this is usually 10–16 weeks in the case of biological treatments. It is also important to consider the effect of treatment on comorbidities. There is evidence that systemic treatments can have a beneficial effect on comorbidities as well as addressing skin symptoms. For example, treatment with TNF antagonists appears to reduce the excess risk of cardiovascular events in patients with rheumatoid arthritis \(^3\).

### Table 1

<table>
<thead>
<tr>
<th>RECOMMENDATIONS FOR MINIMUM TREATMENT GOALS IN TREATING MODERATE-TO-SEVERE PSORIASIS (monotherapy or combination treatment)</th>
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<tbody>
<tr>
<td><strong>I. At the end of induction treatment</strong></td>
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<tr>
<td>– PASI 50 and DLQI &lt; 5</td>
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<tr>
<td><strong>II. Long term symptom control (monitored every 4 to 8 weeks)</strong></td>
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<tr>
<td>– PASI 50 and DLQI &lt; 5</td>
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<tr>
<td><strong>III. Further treatment goals, if applicable:</strong></td>
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<tr>
<td>– Improvement of psoriatic nail disease</td>
</tr>
<tr>
<td>– Consideration of associated diseases (perhaps interdisciplinary diagnostics and treatment)</td>
</tr>
<tr>
<td>– Consideration of psoriatic arthritis (perhaps interdisciplinary diagnostics and establishing treatment goals, e.g. ACR 50, prevention of progression and bone changes)</td>
</tr>
</tbody>
</table>

Source: Reich R, Mrowietz M. J Deutsch Derm Gesell 2007;5:566–574

Patients with psoriasis should be regularly assessed for comorbidities. Psoriasis is an independent risk factor for myocardial infarction, Prof. Sterry noted. Blood pressure,
bodyweight, BMI and waist circumference should be assessed yearly, and in obese patients fasting glucose and blood lipids should also be assessed. Patients with metabolic syndrome should be given lifestyle advice on reducing their cardiac risk. Elevated blood lipids and hypertension should be treated. Rigorous treatment of systemic psoriatic inflammation may also decrease cardiovascular risk. However, physicians need to be vigilant for comorbidities caused by antipsoriatic drugs themselves.

Certain drugs act as triggers for psoriasis, notably beta blockers, lithium and hydroxyquin/chloroquin. It is likely that NSAIDs, ACE inhibitors, tetracycline, interferons and terbinafin can also be triggers. It is therefore important to check whether patients are taking any of these medications.

Improving the care of psoriasis requires a comprehensive approach to the patient, Prof. Sterry said in summary. Treatment goals need to be defined and treatment should be in line with up-to-date guidelines. Patients should be referred to other disciplines where appropriate.

Are we optimising the use of systemic therapies in psoriasis?

In a recent survey of 90 dermatologists in the US, Patel and colleagues found that systemic treatments or biologics were prescribed for only 56% of the most severe patient. Around half of patients with an affected body surface area of greater than 40% were left without any systemic treatment. This and other studies support the conclusion that a substantial number of patients with moderate-to-severe psoriasis are still undertreated, said Peter van de Kerkhof (Radboud University, Nijmegen, the Netherlands).

There are safety concerns over long-term use of conventional systemic therapies: skin cancer and premature ageing with phototherapy; teratogenicity, hyperlipidaemia and mucocutaneous toxicity with retinoids; bone marrow suppression, GI adverse events and hepatotoxicity with methotrexate; and hypertension, renal toxicity and raised cancer risk with cyclosporine. The conventional options for maintenance treatment are methotrexate, retinoids and fumarates, which are all associated with cumulative toxicity. It is very important to follow national or international guidelines when considering long-term treatment with these agents.

Biological agents now offer important new options for maintenance treatment, as well as clearing disease effectively. Evidence is growing year by year that biological therapies offer safe long-term control of psoriasis, Prof. van de Kerkhof said. These agents do have some side effects, but they do not appear to have the cumulative toxicity potential of conventional systemic therapies.

Efficacy and tolerability findings for the conventional systemic treatments vary widely between studies. Similarly, efficacy results obtained with the different biological agents are not directly comparable because of differences in study populations and design. There is a need for comparative studies between the various treatments, but few have been carried out. The first head-to-head comparison between a biological agent and a standard systemic therapy in psoriasis was CHAMPION, a randomised, double-blind, double-dummy trial comparing adalimumab (40 mg every other week), methotrexate and placebo in 271 patients over 16 weeks. The primary endpoint was percentage of patients achieving PASI 75 response at 16 weeks.

Almost 80% of patients receiving adalimumab achieved PASI 75, compared with 35.5% of those receiving methotrexate (p < 0.001) and 18.9% of those receiving placebo (p < 0.001) (Figure 1). Response to adalimumab was rapid, with a mean per cent PASI improvement of 57% achieved at week four, compared to baseline. Seventy-three per cent of patients taking adalimumab had physician assessments of their psoriasis of ‘clear’ or ‘minimal’ compared with 30% of patients taking methotrexate (p < 0.001) and 11% of patients taking placebo (p < 0.001) at week 16. There were no significant differences in the overall incidence of adverse events, serious adverse events or infectious adverse events between the adalimumab, methotrexate and placebo groups during the study period.

The use of systemic treatments in psoriasis is far below optimal, Prof. van der Kerkhof said in his conclusion. Their use can be improved by optimal adherence to guidelines, realistic appreciation of side effect potentials, and insights into efficacy and safety from comparative studies. The role of conventional systemic treatments is likely to reduce dramatically as evidence of long-term safe control with biological agents grows. However, conventional agents such as retinoids or fumarates may remain the best option in patients for whom long-term immunosuppression is undesirable.
Psoriasis patients: a long-term view

Managing psoriasis requires a long-term strategy, as most patients will suffer from the disease throughout their lives. Very few patients with moderate-to-severe disease go into spontaneous remission. Around 20-25% of patients will require long-term systemic therapy, said Christopher Griffiths (University of Manchester, Salford, UK). Without adequate treatment psoriasis has a severe impact on quality of life and physical and psychological wellbeing.

Because the disease is life-long, continued remission after successful treatment is as important as achieving the initial remission, Prof. Griffiths emphasised. However, conventional systemic agents cannot achieve long-term clearance of the disease without a significant risk of cumulative toxicity. In the past the risk of toxicity was reduced by rotating between different systemic agents, or by using agents intermittently and allowing the disease to relapse before restarting treatment. Neither of these strategies is satisfactory for patients; in particular, knowing that the disease will relapse is likely to cause anxiety.

Pharmacogenomic analysis is also being used to minimise the risk of long-term systemic therapy; the aim is to identify the genetic variations that are associated with good response and good tolerability for a particular agent, and target the treatment to patients who are most likely to benefit. This ‘personalised medicine’ approach has been used with methotrexate and is also likely to play an increasing role in the ‘personalised medicine’ approach has been used with methotrexate and is also likely to play an increasing role in treatment decisions with biological agents, said Prof. Griffiths.

Data is now emerging on the long-term efficacy of biological agents: for example, with efalizumab about 40% of patients achieved PASI 75 at 3 months, and all were able to maintain good tolerability for a particular agent, and target the treatment to patients who are most likely to benefit. This ‘personalised medicine’ approach has been used with methotrexate and is also likely to play an increasing role in treatment decisions with biological agents, said Prof. Griffiths.

New results from REVEAL trial

New subanalyses from the REVEAL trial, covering therapy interruption, efficacy in different patient subgroups and effects on C-reactive protein, were presented at the Congress. Reveal was a randomised, controlled phase III trial assessing the efficacy and safety of every-other-week dosing of adalimumab in moderate-to-severe psoriasis over 52 weeks [6]. Eligible patients had PASI score ≥ 12, had previously failed topical therapy and had not received anti-TNF therapy before. Patients were initially randomised to receive either adalimumab 40 mg every other week (n = 814) or placebo (n = 398) for 15 weeks (period A). At week 16, 71% (578 of 814) of adalimumab and 7% (26 of 398) of placebo-treated patients achieved at least a 75% improvement in the PASI score (Figure 2). These responders progressed to the next phase of the study (period B), while non-responders entered an open label extension study. At week 33, patients who had initially been randomised to adalimumab and had achieved a PASI 75 response were re-randomised to continue with either adalimumab or placebo (period C). Upon loss of adequate response, patients were eligible to receive adalimumab in the open-label extension phase, as were all patients who completed 52 weeks of the study.

Interrupted therapy

Twenty-eight per cent (68/240) of patients re-randomised to placebo lost adequate response, compared with 5% (12/250) re-randomised to adalimumab (p < 0.001) [9]. Patients who lost adequate response were less likely to achieve their previous efficacy level when adalimumab was restarted than patients who restarted without having lost adequate response. The results suggest that adalimumab therapy should be used continuously in psoriasis treatment, the authors concluded.

Consistency across patient subgroups

As part of the REVEAL trial, subgroup analyses were carried out to assess the effects of age, duration of psoriasis, history of psoriatic arthritis and recent systemic therapy on treatment outcome after 16 weeks [8]. The analysis found that adalimumab was efficacious across all patient subgroups, with none of these characteristics affecting outcome. “These results are very reassuring for dermatologists and are important because they demonstrate that adalimumab is a treatment option that is effective in a broad group of patients with moderate to severe psoriasis,” commented study author Alan Menter (Baylor University Medical Center, Dallas, TX, USA).
Effect of adalimumab on C-reactive protein

C-reactive protein (CRP) is a biomarker of systemic inflammation and a predictor of cardiovascular risk, and is raised in some patients with psoriasis. A post-hoc analysis of data from the REVEAL study evaluated CRP concentration in patients before and after treatment with adalimumab. CRP concentrations were found to be greater in patients with psoriatic arthritis than in those with psoriasis alone. Adalimumab treatment significantly reduced CRP concentrations, regardless of the presence of psoriatic arthritis or obesity. The mean change from baseline in CRP was -1.3 mg/L for patients who received adalimumab compared with a mean rise of 0.3 mg/L for patients receiving placebo (p < 0.001). Among patients with no psoriatic arthritis who had elevated CRP at baseline, 53 of 82 (64.6%) of adalimumab-treated patients had normal CRP at week 16, compared with 13 of 39 (33.3%) of placebo-treated patients (p < 0.01).

Psoriasis: the burden for healthcare systems and patients

The full extent of the burden of psoriasis on patients and healthcare systems in Europe is not known. The epidemiology, resource utilisation and out-of-pocket costs of the condition were assessed using data from the 2007 EU National Health and Wellness Survey, an annual internet-based survey of a representative sample of adults from France, Germany, Italy, Spain and the UK. The survey was completed by 53,524 respondents, of whom 4% reported a physician’s diagnosis of psoriasis. This would translate into about 9.8 million affected adults in the EU. Of the respondents with psoriasis, 75% reported mild disease and 25% (598) reported moderate-to-severe disease. People with psoriasis were significantly more likely to have been hospitalised than non-PS sufferers, and visited their doctors significantly more frequently. Forty-seven per cent of psoriasis patients had out-of-pocket health expenses: these totalled €1,248/year on average for those with severe disease and €894/year for those with mild disease.

People with moderate-to-severe psoriasis report significantly greater mean total healthcare utilisation than mild- or non-PS sufferers, and have significantly higher out-of-pocket health expenses, the authors concluded. This indicates that the disease is a substantial burden in the EU on both healthcare systems and patients. Effective treatment of moderate-to-severe disease to substantially reduce disease severity or induce remission might lessen the disease burden.

References


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