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ORIGINAL ARTICLE

Improving clinical trial design in psoriasis: Perspectives from the global dermatology community

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Abstract

Background: Clinical trials to test investigational drugs for the treatment of chronic plaque psoriasis currently lack standards for comparison of efficacy and safety data.The majority of studies do not address the important need for long-term treatment. *Methods*: The International Psoriasis Council (IPC) conducted two surveys of its members to assess the need for gold standards, active comparators, and long-term therapy in clinical trials. In Survey 1, 30 participants delivered viewpoints on active comparators for topical therapy (six questions), systemic therapy (nine questions), and continuous versus intermittent therapy (six questions). In Survey 2, 31 participants provided input on gold standards for treatment (five questions), appropriate comparators (four questions), and continuous versus intermittent therapy (six questions). The IPC leadership interpreted the results after each survey. *Results*: The majority of participants (77% in Survey 1 and 89% in Survey 2) agreed that studies of investigative treatments should include an active comparator. Participants described the most important feature of a gold standard as a treatment that: is widely used and generally accepted (45%); has the best efficacy (42%); and is well tolerated (13%). The majority agreed that gold standards should be dependent on: patient subgroup; location/extent of psoriasis; and psoriasis subtype/morphology. It was also agreed that continuous therapy for more than 3 years is needed for patients with moderate-to-severe plaque psoriasis. We have provided an expert opinion regarding the definition of a gold standard in psoriasis and have also established that no single treatment can be the gold standard across all subgroups and types of the disease. *Conclusions*: A single gold standard for the treatment of psoriasis does not exist. The complexity and heterogeneity of psoriasis requires different gold standards for the various manifestations of psoriasis and for subgroups of patients reconciling comorbidities. Of note, 17 experts out of 30 selected methotrexate as the most nominated gold standard amongst systemic agents. The experts support the election of an active comparator as one that is most efficacious over just the best in a particular class. In concordance, 87% of respondents agreed that good tolerability is therefore not the lead criterion for selection of an active comparator in favor of effectiveness and broad use. Patients with moderate-to-severe plaque psoriasis require continuous therapy; this statement was supported by 93% of the experts. Reasons for considering long-term therapy included appearance of comorbidities, impairment of quality of life, possibility of relapse, and subjective complaints such as itch, pain, and joint disease.

Key words: *clinical trials, control groups, investigational drugs, psoriasis*

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Introduction

With increased understanding of the pathogenesis and genetics of psoriasis, several new therapies for the treatment of the disease have become available in the past decade, including tumour necrosis factor (TNF) antagonists, T-cell inhibitors, and anti-interleukin (IL)-12/IL-23 therapy (1). Multiple cytokine-specific new therapies are also in various stages of clinical trial (2). All new agents must be tested in human clinical trials of appropriate design and statistical power. The design of clinical trials is critical for the interpretation of efficacy and safety data; study outcomes must be selected so that data can be compared to other studies and placed in the context of real world practice.

In a review of randomized, controlled trials (RCTs) to test psoriasis therapies from 1977 to 2006, Naldi and colleagues found that the number of head-to-head trials had decreased, while the number of trials using a placebo control has increased by 55% (3). Only 8% of recent studies included a measure to examine quality of life in patients with psoriasis. The median duration of recent clinical trials was 12 weeks. The findings of this study highlight the need for improvements in clinical trial design to address the need for useful active comparators for new therapies (not placebo) and take into account the long-term nature of the disease within the study design.

The International Psoriasis Council (IPC) is a global, non-profit organization dedicated to advancing psoriasis research and treatment by providing a forum for education, collaboration, and innovation among physicians, researchers, and other professionals involved in psoriasis.

Methods

The IPC Board of Directors met with the European Medicines Agency (EMA) in January 2008 to identify areas of common interest with respect to psoriasis treatments. Two areas were identified: active comparators in clinical trials and the need for continuous versus intermittent therapy. The IPC developed a questionnaire (Survey 1) to address these issues. The questionnaire was administered to the membership of the IPC, which comprises psoriasis experts from 16 countries who must be voted into the post, by the board of the IPC, based upon their contributions to the field of psoriasis. The participants were asked about active comparators for topical therapy (six questions) and systemic therapy (nine questions), and continuous versus intermittent therapy (six questions). The IPC leadership discussed the study results and identified additional issues that were raised by the study results. The IPC subsequently developed a follow-up questionnaire (Survey 2) regarding a gold standard for treatment (five questions), appropriate comparators (four questions), and continuous versus intermittent therapy (six questions). A second consensus conference was held in July 2009 to discuss the results of the two questionnaires.

To view the questionnaires please visit www.psoriasiscouncil.org

Results

Thirty of 46 questionnaires from Survey 1 and 31 of 51 questionnaires from Survey 2 were completed and returned; response rates of 65% and 61%, respectively.

Gold standard for treatment

General question: Is there a gold standard for topical therapy? If yes, please identify; if no, please list your first three choices. For topical therapies, 37% of participants in Survey 1 responded that there is a gold standard available for treatment. Of these participants, those who identified a gold standard suggested high-potency topical steroids (n = 6), calcipotriol plus betamethasone dipropionate (n = 4), and anthralin (n = 1). Participants (63%) who answered that there is not a gold standard were asked to submit their top choices for a standard, which included calcipotriol or vitamin D analogs (n = 7), clobetasol propionate or corticosteroids (n = 5), calcipotriol plus betamethasone dipropionate (n = 4), and triamcinolone acetonide (n = 1).

When asked if there is a gold standard for systemic therapies, 23% responded yes; these participants identified methotrexate (n = 3), etanercept (n = 2), cyclosporine (n = 1), and infliximab (n = 1) as gold standards. Top choices for a gold standard by participants who responded that there is no current gold standard included methotrexate (n = 14), cyclosporine (n = 5), fumarates (n = 3), and TNF antagonists (n = 1).

Question (Survey 2 only): For chronic plaque psoriasis, what should the active comparator represent, assuming that each choice has an acceptable safety profile based on current practice (select one)? Participants described the most important feature of a gold standard as: a treatment that is widely used and generally accepted (45%), a treatment that has the best efficacy (42%), and a treatment that is well tolerated (13%). The

majority agreed that gold standards should be dependent on patient subgroup, location/extent, and psoriasis subtype/morphology (Table I).

Table I. Identification of subgroup, location/extent, and subtype/morphology of psoriasis to be considered independently for a gold standard for psoriasis therapy.

	Participants responding (%)	Most common therapy suggested (*n*)
Subgroup features		
Location/extent of psoriasis	87	
Sub-type of psoriasis	87	
Negative impact on quality of life	60	
Treatment responsiveness	72	
Previous topical corticosteroid failure	25	
Previous vitamin D3 analog failure	28	
Previous phototherapy failure	57	
Previous classical systemic therapy failure	77	
Previous biologic therapy failure	77	
Locations/extent		
Chronic plaque psoriasis on elbows, knees, and sacral region, <10% BSA	71	Topical steroids + vitamin D analogs (10)
Chronic plaque psoriasis, >10% BSA	93	Methotrexate (9)
Scalp psoriasis	78	Topical steroid (15)
Flexural psoriasis	59	Topical steroid (13)
Facial psoriasis	67	Topical steroid (11)
Palmar-plantar psoriasis (plaque)	89	Retinoid/ acitretin (11)
Psoriasis subtypes/ morphologies		
Chronic plaque psoriasis	89	Methotrexate (7)
Guttate psoriasis	68	Phototherapy/ UVB (18)
Erythrodermic psoriasis	82	Cyclosporine (10)
Generalized pustular psoriasis	86	Retinoids/ acitretin (10)
Palmar-plantar pustulosis	86	Retinoids/ acitretin (13)

BSA = body surface area; UVB = ultraviolet B.

Comparators for clinical trials

General question: Should studies of investigational treatments include an active comparator? If yes, what is the suggested active comparator and what are important considerations for an active comparator? The majority of participants (77% in Survey 1 and 89% in Survey 2) agreed that studies of investigative treatments should include an active comparator. Eighty-three percent of participants in Survey 1 agreed that safety profiles should be considered when choosing an active comparator. Assuming that each choice had an acceptable safety profile based on current practice, participants believed that the active comparator should represent the best efficacy of current practice (54%), the best efficacy in class (36%), minimal efficacy in class (7%), or minimal efficacy of current practice (3%). Suggestions for active comparators for investigative therapies are shown in Table II. For randomized trials, participants in Survey 2 proposed the following considerations for the selection of an active comparator: adequate efficacy for the subtype/extent of disease, whether or not comorbidities such as psoriatic arthritis will be monitored, inclusion of a placebo arm, response to previous treatments, dosage of active comparator, and the presence of pruritus.

Continuous versus intermittent therapy

General question: How long is continuous therapy needed and what are the important considerations for continuing or discontinuing continuous therapy? Participants in Survey 1 estimated that the clearing phase required a mean (range) duration of 9 (2–12) weeks for topical therapies and 12 (2–24) weeks for systemic therapies. The maintenance phase required a mean (range) of 28 (8–52) weeks for topical therapies and 35 (12–52) weeks for systemic therapies. In Survey 2, 93% of participants noted that patients with moderate-to-severe plaque psoriasis require continuous therapy. The estimated duration of continuous therapy was similar in both surveys (Table III). The duration of continuous therapy by treatment was also estimated (Figure 1).

Predictors for needing long-term therapy in Survey 1 included: duration of post-treatment remissions (83%), disturbance of quality of life (73%), duration of previous systemic therapies (73%), number of previous systemic therapies (70%), previous systemic therapies (63%), and other reasons (23%). Reasons for considering long-term therapy in Survey 2 included: impairment of quality of life (96%), possibility of disease relapse (85%), appearance of comorbidities (74%), subjective complaints such as pruritus or pain (74%), chronic nature of disease

Table II. Suggestions for active comparators in clinical studies of investigational drugs for psoriasis.

	Survey 1	Survey 2	
Agent	Active comparator (*n*)	Best overall (*n*)	Best in class (*n*)
Vitamin D3 analog		Topical steroid (17)[a]	Calcipotriene (4) Calcipotriol (3)
Topical steroids (potent/superpotent)		Vitamin D3 analog (9) Topical steroid (9)[b]	Clobetasol propionate (5)
Topical steroids (mild)		Vitamin D3 analog (12)	Hydrocortisone (2) Vitamin D3 analog (2)
Topical retinoids		Vitamin D3 analog (10) Topical steroid (9)[c]	
Phototherapy/photochemotherapy/lasers		Methotrexate (8)	NB-UVB (8)
Systemic retinoids/RAMBA	Acitretin (15)	Methotrexate (16)	Acitretin (8)
Systemic calcineurin inhibitor	Cyclosporine (16)	Methotrexate (14)	Cyclosporine (8)
Fumarates	Methotrexate (12)	Methotrexate (15)	Methotrexate (5)
Anti-TNF agent	Etanercept (12)	Methotrexate (13)	Etanercept (6)
Anti-T-cell agent	Efalizumab (9) Methotrexate (8)	Methotrexate (13)	Alefacept (4) Methotrexate (4) Anti-TNF agent (7)[d]
Anti-IL12/IL23 (anti-p40) agent		Methotrexate (9) Anti-TNF agent (13)[e]	Ustekinumab (6) Anti-TNF agent (10)[f]
New biologic agent targeting cytokines	Etanercept (7) Methotrexate (6)	Methotrexate (8) Anti-TNF agent (13)[g]	Methotrexate (5) Anti-TNF agent (9)[h]
New small molecule agent		Methotrexate (12)	Methotrexate (8)

[a]Included unclassified (6), mild (3), mid-potency (3), and potent (5) topical steroids.
[b]Included mild (2), class II (1), class IV (1), clobetasol (2), and comparable class (3) topical steroids.
[c]Included unclassified (5), mild (2), moderate (1), potent (1), class V or VI (1) topical steroids.
[d]Included adalimumab (1), etanercept (3), and unspecified (3) anti-TNF agents.
[e]Included adalimumab (2), etanercept (5), infliximab (1), and unspecified (5) anti-TNF agents.
[f]Included adalimumab (1), etanercept (6), and unspecified (3) anti-TNF agents.
[g]Included adalimumab (2), etanercept (5), infliximab (1), and unspecified (5) anti-TNF agents.
[h]Included adalimumab (1), etanercept (6), and unspecified (2) anti-TNF agents.
NB-UVB = narrow-band ultraviolet B phototherapy; RAMBA = retinoic acid metabolism blocking agent; TNF = tumour necrosis factor; IL = interleukin.

Table III. Estimated length of continuous therapy in patients with moderate-to-severe plaque psoriasis ($n = 60$).

Duration of therapy	Survey 1 (%)	Survey 2 (%)
0.5 years	0	7
1 year	17	15
2–3 years	20	11
>3 years	63	67

(74%), and emergence of arthritis (59%). Responses to an open-ended query of reasons to discontinue long-term treatment (excluding contraindication or major side effects) included: loss of efficacy ($n = 6$), remission ($n = 3$), possible cumulative toxicity ($n = 3$), 6 months without psoriasis lesions ($n = 2$), and one response each of need to assess disease activity, drug holiday, patient opinion of clear/stable psoriasis, patient desire to discontinue, legal concerns, and newer therapy may be better.

Predictors of post-treatment remission in Survey 1 included: phenotype of psoriasis (73%), previous erythrodermic psoriasis (60%), previous pustular psoriasis (57%), duration of psoriasis (43%), and previous treatments (37%). Treatment with psoralen and ultraviolet A (PUVA) and alefacept were estimated to provide the longest duration of post-treatment remission (Figure 2).

Discussion

In consultation with the EMA, the IPC has identified the use of active comparators and the need for intermittent versus continuous therapy as aspects of

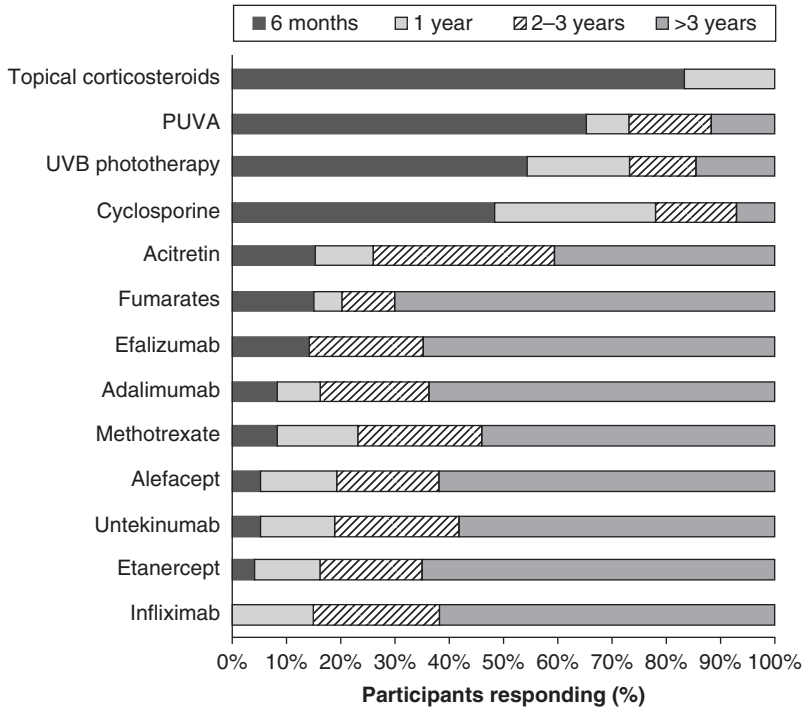

Figure 1. Estimated duration of need for continuous treatment for different psoriasis therapies. Proportion of participants in Survey 2 estimating a duration of 6 months (black), 1 year (light gray), 2–3 years (diagonal lines), and > 3 years (dark gray) of treatment for different psoriasis therapies. (PUVA = psoralen plus ultraviolet A; UVB = ultraviolet B).

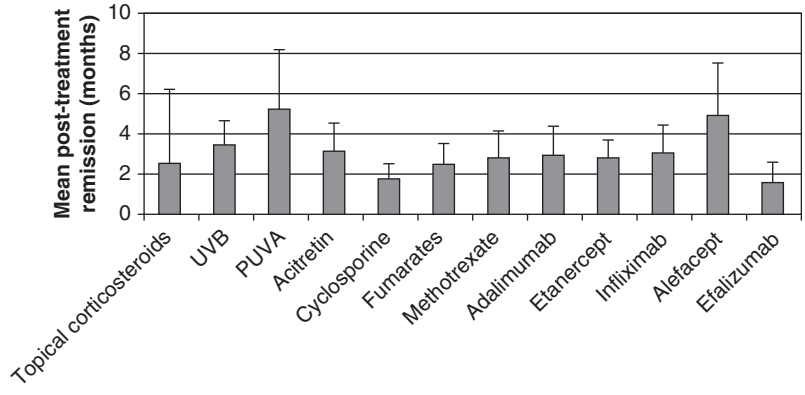

Figure 2. Estimated duration of mean post-treatment remission. The mean duration of remission after treatment in months estimated by participants in Survey 1 are shown. Error bars represent standard deviations. (UVB = ultraviolet B; PUVA = psoralen plus ultraviolet A).

clinical research in psoriasis that should be addressed. Two surveys of psoriasis experts were conducted in an attempt to identify possible comparators and assess the current beliefs and practices with respect to intermittent versus continuous long-term therapy. The study was limited by the small number of participants; however, the participants were all experienced clinicians and had played significant roles in various research studies and guidelines of care related to psoriasis. As a result, it would be expected that their opinions would represent current global beliefs and practices. A second limitation was the limited response options in the questionnaires. To address this issue, the second questionnaire was designed to improve clarity of the options included in the first questionnaire.

The definition of a gold standard for psoriasis therapies has not been established. It was suggested that the definition of the gold standard should be "a therapy that is widely used, generally accepted, and well tolerated, but not necessarily the best in class." Evidence of clinical efficacy is important, but should

not eliminate a candidate gold standard from consideration, as older therapies have not been as rigorously tested in clinical trials as newer therapies. There should also be consideration of how therapies are likely to be used in clinical practice.

Uniform agreement on a gold standard for psoriasis treatments was not achieved. However, over two-thirds of the participants did agree that subgroups of patients (e.g. previous treatment failure of traditional systemic or biologic therapies, etc.), location/extent of psoriasis (e.g. chronic plaque psoriasis >10% BSA, scalp or palmar-plantar psoriasis, etc.), and subtypes/morphologies (e.g. chronic plaque psoriasis, guttate psoriasis, etc.) should be considered independently in the selection of an active comparator or gold standard. Preferred gold standards varied by each of these criteria.

While the majority of participants agreed that investigative studies should include an active comparator, there was no consensus on the criteria to be used for selection of comparators. Approximately half of the participants suggested that the active comparator should have the best efficacy in current practice, while approximately one-third recommended that the active comparator should have the best efficacy in class. Preferred comparators varied when considering best overall versus best in class, and responses varied by country. Methotrexate was suggested as the preferred comparator for phototherapy and systemic therapies. An important consideration when selecting an active comparator is the safety profile.

The US Food and Drug Administration (FDA) and the EMA differ in their stance on control groups in clinical trials. The FDA guidance on control groups describes the purpose and use of placebo and active control groups but does not make specific recommendations for comparators in clinical trials of patients with psoriasis (4). US-based clinical trials of therapies for psoriasis use placebo as a control. Because of the seasonal and fluctuating nature of psoriasis, the EMA recommends the use of a placebo arm to determine study sensitivity (5). A topical placebo (usually test vehicle) should be used as a control for topical treatments and a systemic placebo should be used as a control for systemic therapies. The EMA also recommends that parallel group, double-blind, vehicle and active comparator controlled study designs should be used for therapeutic confirmatory studies.

The majority of participants agreed that continuous therapy is needed for patients with moderate-to-severe plaque psoriasis, and that continuous therapy is needed for more than 3 years. Reasons for considering long-term therapy included impairment of quality of life, the possibility of relapse, and subjective complaints such as itch, pain, and joint disease. Psoriasis is considered to be a chronic, lifelong disease in the majority of sufferers. Thus, because of the waxing and waning nature of psoriasis symptoms and our inability to predict flares, continuous care will out of necessity be required in the majority of patients with moderate-to-severe psoriasis. The length of continuous therapy in clinical practice is dictated by the safety profile of the agent; however, over half the experts suggested using systemic and biologic agents (except for cyclosporine) continuously for more than 3 years. There was a consensus that rotational therapy is not better than the common treatment regimens currently in use.

While the duration of most clinical trials of new agents for psoriasis is relatively short (approximately 12 weeks), many clinical development programs have incorporated long-term, open-label extension studies to these short-term trials. Additionally, the FDA is now requiring long-term post-marketing commitments (e.g. registries) from drug manufacturers to document the efficacy and safety of new systemic and biologic agents for periods up to 5 years. These types of studies provide data on the durability of response and the emergence of rare adverse events in conjunction with the safety of long-term use of agents to treat psoriasis. Thus, they are likely to better represent real world clinical practice.

Issues that required further study were highlighted; these included the use of induction/maintenance therapies, monotherapy versus combination therapy, and need for better definitions of remission (versus durability of response). Phototherapy is an example of an episodic, intermittent treatment, and is a good induction therapy. While remission may be long-lived with the disappearance of clinical symptoms without therapy, it cannot be considered a cure. In addition to standards for testing the efficacy of therapies, clinically useful standards for measures of disease severity and patient-reported outcomes in psoriasis, psoriatic arthritis, and quality-of-life studies need to be developed (6).

In summary, the IPC is working to establish important standards and comparators for clinical trials of investigational drugs for the treatment of psoriasis. Many traditional therapies that are currently in use in clinical practice (e.g. methotrexate) were not tested in rigorous clinical trials that are used to evaluate drugs today. The lack of robust efficacy and safety data for older agents poses a challenge in the selection of gold standards and active comparators, as these older agents represent a large proportion of clinical experience. The complexity and heterogeneity of psoriasis requires different gold standards for the various manifestations of psoriasis

and for subgroups of patients with comorbidities. Methotrexate was nominated by the majority of experts as the gold standard amongst all systemic agents. The experts support the election of an active comparator as one that is most efficacious over the best in a particular class. There is clearly a need for safe, long-term, continuous therapy for the majority of patients with chronic plaque psoriasis, especially those with moderate-to-severe forms of the disease. This statement was supported by 93% of the experts. Appropriate standards and comparators and the need for long-term therapy should be considered in the design of clinical trials to test new investigational agents.

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