Psoriasis, a proof-of-principle condition for immune-mediated inflammatory disorders: perspectives toward optimal clinical trial design

Therapeutic agents with a putative anti-inflammatory mode of action are increasingly being pilot tested in psoriasis, a chronic inflammatory systemic disease. This is because the psoriasis patient contributes a number of advantages to trial design and execution (e.g., high disease prevalence, homogenous patient characteristics, skin manifestation that supports quick and easy quantification and viable placebo controls). Trial design for psoriasis is relatively standardized. Chronic plaque-type psoriasis usually follows a stable clinical course and also has well-accepted inclusion and exclusion criteria. Since psoriasis disease activity is characterized by lesions and percentage of the body area affected, there are multiple acceptable study end points that afford quantification of therapeutic impact, including quality of life, in the absence of a need for surrogate or biomarkers. Limitations of the psoriasis clinical trial framework are also apparent (e.g., multiple psoriasis phenotypes or capacity to evaluate across the complete disease severity spectrum), which means the population is not broadly applicable to all clinical trials destined to study agents that might impact psoriasis and/or systemic inflammation. Thus, psoriasis is a proof-of-principle condition with multiple opportunities for further research in developing potential treatments for a larger proportion of the population with psoriasis and other immune-mediated inflammatory disorders.

Keywords: Physicians Global Assessment • psoriasis • Psoriasis Area and Severity Index • quality of life • systemic inflammation

Psoriasis: a proof-of-principle disease

Over the past two decades, substantial progress has been made in the management of a variety of chronic immune-mediated inflammatory diseases, including rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis and psoriatic arthritis [1–4]. While the first biologic therapies, particularly the TNFα inhibitors, were initially tested in these disease states and only later transitioned to psoriasis, the relative appeal of conducting psoriasis studies has changed this paradigm. Now, multiple agents including abatacept, p40 inhibitors, IL-17 antibodies and JAK-STAT inhibitors have been, and are being, pilot tested in psoriasis [5,6]. The reason for this shift is multifactorial. Psoriasis is common, affecting approximately 1–3% of the population worldwide, and therefore there is no shortage of subjects for clinical trials [7,8]. Also, since disease manifests on the skin, efficacy end points are determined by visual assessment of lesion severity, and are therefore noninvasive and relatively easy to detect. End point measurements can be quantified rapidly, typically within 12–16 weeks, thus precluding the need for lengthy trials to demonstrate...
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meaningful outcomes [14]. Although psoriasis patients suffer from multiple medical comorbidities, such as the metabolic syndrome, inflammatory bowel disease and depression, at rates higher than the general population, they tend to be relatively healthy, albeit obese, and functionally compared to patients with other chronic inflammatory diseases [21]. A placebo arm can thus be readily included into the clinical study. Although placebo effect improvements are significant in psoriasis clinical trials (ranging from 15 to 20%) [10], the efficacy of many therapies is readily quantifiable relative to placebo, with improvements of 50–75% being commonly observed and over 90% achievable. Collectively, these factors support the utility of utilizing psoriasis as an ideal ‘proof-of-concept’ condition for immunology research and drug development. In the following sections, we will focus on outlining the optimal design characteristics and framework for clinical trials of systemic therapies in psoriasis.

Design characteristics of psoriasis clinical trials

The first step in designing any clinical trial involves identifying the research question (i.e., the hypothesis being tested). Once the research question is posed, study objectives can be formulated. Well-constructed objectives are critical as they guide subsequent trial design. In the case of psoriasis clinical trials, especially involving systemic therapies, the primary objectives relate to validation of treatment safety and quantification of treatment efficacy, generally defined as improvement in patients’ skin lesions and quality of life (QOL). Several other factors in trial design also need to be considered.

Population selection

Choosing the appropriate study population in which to test and demonstrate outcomes of an experimental therapy is an important design element in all clinical trials, including psoriasis. In trials of systemic biologic agents, patients with moderate to severe chronic plaque psoriasis are chosen for several reasons. Plaque-type phenotypical presentation is the most common subtype of psoriasis (representing 70–80% of patients), tends to possess a more stable clinical course than other forms of psoriasis, and may be managed with placebo for defined durations of time without significant patient risk [14, 16]. Moderate to severe levels of disease severity are also required in order to justify the use of a systemic immunomodulatory agents with the concomitant potential risks [16, 17]. Inclusion of moderate to severe patients also allows for a demonstration of treatment differences relative to placebo versus mild patients. In addition, the study of a homogeneous group of patients relative to disease severity is preferable to support statistical separation of therapeutic effect. To help identify and enroll eligible patients meeting healthcare and clinical standard and rigorous manner, clear inclusion and exclusion criteria are specified. Typical inclusion criteria include an established diagnosis of psoriasis for at least 6 months and a Psoriasis Area and Severity Index (PASI) ≥ 10 or 12, body surface area (BSA) involvement ≥ 10 and Physician Global Assessment (PGA) ≥. Exclusion criteria usually include a history of malignancy (not in remission), many factors that could result in severe chronic or recurrent infectious disease, or other major medical conditions [34]. Adherence to these criteria ensures enrollment of psoriasis patients with moderate to severe disease appropriate for systemic therapy.

Study architecture

Psoriasis trials of systemic medications are frequently conducted across multiple centers and employ randomization, double blinding and a placebo control. The majority of trials evaluating a novel therapy for moderate to severe chronic plaque psoriasis will choose a placebo arm as a control. Indeed, selected regulatory bodies (i.e., the US FDA) tend to require a placebo arm for approval whereas other organizations (e.g., the European Medicines Agency) are transitioning to rapidly transition to the use of active comparator arms in the case of high disease burden therapies. As such, the potential for a significant flare of psoriasis during placebo controlled trials is relatively low. Patients are transitioned to the active arm of the study in longer Phase III studies after a placebo period of approximately 12 weeks [16]. Lengthy trials might cause patients on placebo to endure suffering that will require secondary treatments [3]. In cases where a current therapeutic standard exists, the test therapy must then be compared to this accepted standard of care. A potential disadvantage of such an active comparator design is the relatively large enrollment requirement to statistically detect an efficacy difference between the two active agents, especially if statistical superiority is sought. Statistically, the number of patients necessary is inversely proportional to the expected treatment difference between the two active agents. Thus, a smaller anticipated differential necessitates a higher and more costly enrollment. A non-statistical result in such a trial design confounds the interpretation and validity of the study. Consequently, noninferiority trial designs may be preferred [2]. These are applicable when a placebo-controlled trial is not ethically feasible (placebo cannot be used) or when the treatment under test is not expected to be much better than current standard of care. However, these trials may not rule out the presence of a treatment effect in secondary end points, safety, costs, compliance or convenience. Clinical significance is more readily attained in placebo trials relative to comparative trials, translating into decreased trial size and cost [22]. Thus, many psoriasis pharmaceutical companies frequently require comparative data in order to delineate relative economic benefits to support approval and reimbursement of new therapies.

Choosing the appropriate study population in which to test and demonstrate outcomes of an experimental therapy requires careful selection when planning the study. The majority of trials evaluating a novel therapy for moderate to severe chronic plaque psoriasis will choose a placebo arm as a control. Indeed, selected regulatory bodies (i.e., the US FDA) tend to require a placebo arm for approval whereas other organizations (e.g., the European Medicines Agency) are transitioning to rapidly transition to the use of active comparator arms in the case of high disease burden therapies. As such, the potential for a significant flare of psoriasis during placebo controlled trials is relatively low. Patients are transitioned to the active arm of the study in longer Phase III studies after a placebo period of approximately 12 weeks [16]. Lengthy trials might cause patients on placebo to endure suffering that will require secondary treatments [3]. In cases where a current therapeutic standard exists, the test therapy must then be compared to this accepted standard of care. A potential disadvantage of such an active comparator design is the relatively large enrollment requirement to statistically detect an efficacy difference between the two active agents, especially if statistical superiority is sought. Statistically, the number of patients necessary is inversely proportional to the expected treatment difference between the two active agents. Thus, a smaller anticipated differential necessitates a higher and more costly enrollment. A non-statistical result in such a trial design confounds the interpretation and validity of the study. Consequently, noninferiority trial designs may be preferred [2]. These are applicable when a placebo-controlled trial is not ethically feasible (placebo cannot be used) or when the treatment under test is not expected to be much better than current standard of care. However, these trials may not rule out the presence of a treatment effect in secondary end points, safety, costs, compliance or convenience. Clinical significance is more
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and combines this with the percentage of BSA covered. This assessment facilitates the categorization of psoriasis lesions into eight grades, from clear to very severe. The lattice system provides a static step score that has meaning for both doctors and patients [29,32].

■ QOL

Although studies using inter-rater reliability as a measure ranked the PASI with 'substantial' reliability and the PGA with 'substantial' or 'moderate' reliability, these inter-rater reliability determinations to the PASI and PGA, as they do not capture the substantial impact of disease on a patient's QOL. The visibility of the disease process can have an emotional impact that exceeds physical pain and suffering in its severity. Lesions on sensitive areas such as the face or genitals make it difficult to develop personal relationships, and frequently cause stigmatization, loss of self-confidence and even depression [33]. Lesions in mechanically sensitive areas such as the face or genitals make it difficult to develop personal relationships, and frequently cause stigmatization, loss of self-confidence and even depression [33]. Lesions in mechanically sensitive areas such as the face or genitals make it difficult to develop personal relationships, and frequently cause stigmatization, loss of self-confidence and even depression [33].

Once safety and tolerability are demonstrated, Phase II studies are conducted to further confirm safety, and also to evaluate efficacy. Trials for moderate to severe psoriasis typically include clinical measures such as achieving a 50 or 75% reduction in PASI or PGA score of clear (0) or minimal (1) as primary end points. QOL assessments such as achieving a 0 or 1 in DLQI are also utilized, usually as secondary outcome measures [41]. Phase III trials evaluating moderate to severe chronic plaque psoriasis typically utilize similar end points as Phase II studies, but with a much larger group of patients, typically in the thousands. Primary end points focus on PASI reduction of 50 or 90% [41,44] or static PGA of clear or minimal and secondary end points include further safety testing and QOL measures. Phase II trials are generally statistically powered to demonstrate a difference in efficacy as measured by the primary end point between active and placebo or comparator groups. Often because of efficacy of some agents, Phase III trials are powered for general safety and may be overpowered for efficacy. It should be noted that these randomized controlled trials are not sufficient to detect rare but serious events that often only show up after many years. The phase of the trial and the known safety data for the investigational agent. Generally, Phase I and II studies (usually up to 12–16 weeks in duration) involve more frequent visits, while Phase III and open-label studies, often 52 weeks in duration, have longer intervals between visits. At follow-up visits, clinical efficacy end points (usually consisting of PASI, PGA and QOL measures as discussed above) and safety measures (including ECG, laboratory values and a physical examination) are re-assessed and compared to baseline values. For safety and data collection purposes, the final study visit should be completed for all subjects, even if they withdraw from the study before the end of the trial. This visit usually consists of a full physical examination, as well as the appropriate laboratory tests and relevant assessments. The final visit closes the screening and baseline visits, in order to fully document the subject's status and the disease progression throughout the trial. In order to ensure sufficient data collection throughout the trial, Case Report Forms are supplied by the study sponsor for the investigator to complete and return to the sponsor on a regular basis. This becomes especially important in large, multicenter trials, where it is essential to standardize data collection across all sites. The Case Report Forms ensure that the protocol is being followed and that all data are collected and evaluated for each end point in a consistent manner.

If a study drug is promising and the benefits appear to outweigh the risks, an extension trial may be conducted in order to test the drug's safety and efficacy over a longer period of time (3–9 years). Subjects are eligible to continue in an extension study at the end of the trial, and if well planned, the subject will be able to receive the study medication in an ongoing study without dose interruption.

■ Subject recruitment

Centers conducting clinical trials frequently have a registry of subjects who have participated in a prior study and will potentially be eligible for future studies. Depending on the size and experience of the center, this adds a considerable resource for recruitment. Academic hospital-based dermatology clinics and private practices with a research facility are valuable resources for clinical trial subjects. Creating a relationship with these groups and keeping them informed about current or future studies allows for easier and more stable recruitment. Flyers and advertisements can also be distributed to the various hospital facilities and posted in community centers, and other high-traffic areas together with advertising in newspapers, radio and television. Craigslist and other relevant internet sites, as well as social networking sites such as Facebook and Twitter, are now being used frequently for study recruitment.

All patients selected for inclusion are re-examined at a second baseline visit to confirm eligibility and success of washout. Baseline safety ECG and laboratory results are collected. A baseline PASI or PGA value for subjects at day zero is also determined to compare against subsequent values during the administration period of the study agent. The subject is then randomized to a study arm and the first dose of study agent is administered at this visit. Subjects are usually issued a diary to record their use of the study drug between visits [44].

The frequency of follow-up visits varies based on the phase of the trial and the known safety data for the investigational agent. Generally, Phase I and II studies (usually up to 12–16 weeks in duration) involve more frequent visits, while Phase III and open-label studies, often 52 weeks in duration, have longer intervals between visits. At follow-up visits, clinical efficacy end points (usually consisting of PASI, PGA and QOL measures as discussed above) and safety measures (including ECG, laboratory values and a physical examination) are re-assessed and compared to baseline values. For safety and data collection purposes, the final study visit should be completed for all subjects, even if they withdraw from the study before the end of the trial. This visit usually consists of a full physical examination, as well as the appropriate laboratory tests and relevant assessments. The final visit closes the screening and baseline visits, in order to fully document the subject's status and the disease progression throughout the trial. In order to ensure sufficient data collection throughout the trial, Case Report Forms are supplied by the study sponsor for the investigator to complete and return to the sponsor on a regular basis. This becomes especially important in large, multicenter trials, where it is essential to standardize data collection across all sites. The Case Report Forms ensure that the protocol is being followed and that all data are collected and evaluated for each end point in a consistent manner.
Conclusion & future perspective
Psoriasis is a proof-of-principle condition with multiple opportunities for further research in developing potential treatments for a large proportion of the population with other immune-mediated inflammatory disorders. Subjects with psoriasis tend to be relatively healthy, and the ability to include placebo control is advantageous for drug developers. Furthermore, well-validated tools exist to demonstrate clinical efficacy and QOL improvement such as the PASI, PGA, and DLQI.

Future directions for improving clinical trials in psoriasis include developing a psoriasis-specific QOL tool as recently proposed with the Comprehensive Appraisal of Life Impact of Psoriasis (CALIPSO) [21]. Treatment efficacy is currently measured by a variety of assessment tools and progress continues to be made in improving and validating these tools toward enhancing the evaluation of developmental trends in the clinic [1]. Additionally, the major focus to date has been on the design of clinical trials for chronic plaque psoriasis, which constitutes over 80% of the total psoriasis population. But clinical trial designs cannot be readily applied to evaluate for other forms of psoriasis, including erythrodermic, guttate, pustular, and inverse psoriasis. The development of predictive biochemical or genetic markers that correlate with clinical severity in all of these conditions is needed. In addition, the growing body of evidence regarding the psychological, psychosocial and physical comorbidities specific to psoriasis patients provides new avenues for future end points beyond clinical improvement of lesions. For example, agents that result in decreased systemic inflammation, possibly leading to a decreased risk of cardiovascular disease, which is not uncommonly seen in the psoriasis population, would have clear advantages.

Psoriasis is a constant, chronic, systemic inflammatory disorder that tends to manifest on the skin in people of all ethnic backgrounds. Consequently, its accessibility for measurement facilitates unbiased assessment of therapeutic benefit, a finding that is frequently translatable to other related systemic immune-mediated inflammatory diseases. The underlying immunopathology of psoriasis is correlated with the altered regulation of various cytokines such as TNFα, IL-23 and IL-17. This inflammatory process connects psoriasis to a whole spectrum of associated diseases, the ‘immune-mediated inflammatory diseases’, a group that also includes rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis, psoriatic arthritis, Behcet’s disease and other conditions of autoimmune origin. Since psoriasis is now established as a model disease in this group, therapeutic agents, such as therapeutic antibodies, can initially be evaluated efficiently in psoriasis and then subsequently developed for related immune-mediated inflammatory diseases that are more complicated [14,21]. This psoriasis should be considered the pre-eminent proof-of-concept model for any candidate therapy with a potential anti-inflammatory mode of action.

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Papers of special note have been highlighted as: of considerable interest
24 Excellent evaluations in clinical trials of psoriasis severity and outcome currently in use and assess their reliability with known psoriatic criteria. The authors conclude that none of the psoriasis measures are adequately validated and, thus, the most suitable measures will continue to be validated or call for different measures. 25 Van De Kerkhof PC. The Psoriasis Area and Severity Index and other alternative approaches for the assessment of severity: past, present and future. Br. J. Dermatol. 157(4), 661–666 (2007).
26 Ashcroft DM, Wain AL, Williams HC,


27 The EU consensus Delphi program was performed to define goals for treatment of plaque psoriasis with systemic therapy and to improve patient care. For psoriasis clinical trials of systemic therapies, two phases were identified; an induction phase of up to 16 weeks and a maintenance phase defined as the treatment period after the induction phase. Specific treatment goals were based upon the change of Psoriasis Area and Severity Index (PASI) from baseline to the time of evaluation and the absolute Dermatology Life Quality Index. Implementation of treatment goals in the daily management of psoriasis will improve patient care and mitigate the problem of undertreatment.


29 Determines the degree of correlation between two commonly used psoriasis assessment tools, the PASI and Physician’s Global Assessment (PGA). The R² values for the correlation between PASI 75 and a score of clear or almost clear on the PGA were 0.9157 at 8–16 weeks and 0.892 at 17–24 weeks. Thus, the two assessment tools are substantially redundant and either alone is sufficient for assessing psoriasis severity in patients with moderate-to-severe disease. Since the PASI is better validated and more detailed, it remains the score of choice for clinical trials, but the simpler PGA may be well suited for community-based outcomes projects.


46 Guenther LC, Poulin YP, Pariser DM. A comparison of tazarotene 0.1% gel once daily plus mometasone furoate 0.1% cream once daily versus calcipotriene 0.005% ointment twice daily in the treatment of plaque psoriasis. Clin. Ther. 22(10), 1225–1238 (2000).


52 This clinical study (180 patients) correlated assessment tools for evaluating the severity of skin, nail and joint symptoms in patients with psoriasis and psoriatic arthritis. Overall, correlations were seen between hands and feet, face and scalp, and buttocks, chest and back. However, only low correlation was seen between items assessing joint symptoms with items assessing skin symptoms. These data support the notion that the complex phenotype of psoriatic disease requires instruments that independently assess the severity of skin, nails and joints.

53 Websites
