CLINICAL INVESTIGATION

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

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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

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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 [9,10]. 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 functional compared to patients with other chronic inflammatory diseases [11,12]. 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%) [13], 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 and conduct. 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 are required in order to justify the use of a systemic immunomodulatory agents with the concomitant potential risks [15,17]. Inclusion of moderate to severe patients also allows for easier observation of treatment differences relative to placebo versus mild patients. In addition, the study of a homogenous group of patients relative to disease severity is preferable to support statistical separation of therapeutic effect. To help identify and enroll eligible patients meeting this description in a standard and rigorous manner, clear inclusion and exclusion criteria are specified. Typical inclusion criteria require an established diagnosis of psoriasis for at least 6 months, a Psoriasis Area and Severity Index (PASI) ≥10 or 12, body surface area (BSA) involvement ≥10% and Physician Global Assessment (PGA) ≥3. Exclusion criteria usually include a history of malignancy (non-melanoma skin cancers excluded), chronic or recurrent infectious disease, or other major medical conditions [15]. 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 increasingly mandating a comparator control arm. 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 [15]. Lengthy trials might cause patients on placebo to endure suffering that will require secondary treatments [18]. 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. 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 that much better in terms of efficacy, but may provide alternative effects in secondary end points, safety, costs, compliance or convenience. Clinical significance is more readily attained in placebo trials relative to comparator trials, translating into decreased trial size and cost [19,20]. However, both regulatory bodies and healthcare payers frequently require comparative data in order to delineate relative economic benefits to support approval and reimbursement of new therapies.

Once design and control questions have been decided, calculating a power analysis is paramount. Such an analysis allows investigators to determine the subject sample size necessary to demonstrate statistical significance, which in turn influences many factors that drive the cost and potential success of a study. For example, an efficacious agent that produces a mean percent PASI improvement difference of 45 points between placebo and treatment group may require as few as eight subjects in each group to demonstrate statistical significance in efficacy. On the other hand, demonstrating the safety of an agent requires much greater sample sizes. Indeed, the FDA commonly requires a certain level of exposure of a new agent prior to approval and this might vary with the condition under study according to prevalence, severity and unmet need. To prove a test agent is safe requires the analysis of rare, but potentially severe events. If these events occur at a rate of less than 1/1000 persons per year in the population studied, many more subjects are needed to observe any changes in that signal. Practically, Phase III clinical trials in psoriasis often include several hundred subjects to demonstrate necessary safety outcomes. Even then examples of rare events may not show up until years after a therapies first regulatory approval, as was the case with efalizumab and the appearance of progressive multifocal leukoencephalopathy [21].

■ Scoring systems

Since psoriasis is not a disease that requires diagnosis or monitoring through invasive testing or biomarker tracking [22], disease activity is characterized by the characteristics of lesions and percentage of the body area affected. However, there are some studies demonstrating changes in C-reactive protein levels, an inflammatory marker more likely to be elevated in patients with psoriatic arthritis. Other studies have looked at genomic expression patterns in biopsies of skin and shown the same differentiation in inflammatory patterns, which may ultimately generate some predictive value about efficacy in early-phase studies. The PASI and PGA are two scoring systems that take into account key features of erythema, scale and induration, and have been used in almost all modern trials for psoriasis [23,24]. A review of the instruments used to grade the clinical severity of psoriasis found the PASI to be the most studied and thoroughly validated [25]. However, both PASI and PGA have been shown to be equally sensitive and useful in detecting changes in moderate to severe disease [26,27]. That said, both the EMA and FDA do not utilize the PASI end point for approval purposes. EMA has stated that in some cases the correlation between PASI score and psoriasis severity is not linear, thus confounding the assessment. EMA published guidelines for psoriasis clinical trials in 2004 [101].

Though originally developed by Fredriksson and Pettersson for a specific study in 1978 [28], the PASI quickly became the most often used tool for evaluation of moderate to severe disease and is preferred by some investigators [29,30]. The PASI evaluates the total body in four sections: head, upper extremities, trunk and lower extremities. First, the percentage of area involvement of each body section is estimated to provide the BSA percentage. The percent of that particular body section is graded from 0 (clear) to 6 (>90% covered). The affected areas from each body section are then rated in severity based upon the average redness, thickness and scaling within the lesions from 0 to 4 (4 being most severe). The severity scores are summed and then multiplied by the area involvement score for each body section. The resulting product is multiplied by the area weight (head 0.1, upper limbs 0.2, trunk 0.3, lower limbs 0.4). These values are added together resulting in a final score ranging from 0 to 72 [31]. The average PASI score in the majority of clinical trials in moderate to severe psoriasis is approximately 20, with the average BSA in the 25% range.

In contrast to the complex formulation of the PASI, the PGA system generalizes the extent of the disease and distills it to a single number [32]. Different versions of the PGA exist with scales ranging from 0 to 10 points. A commonly used version ranges from 0 (defined as 'clear') to 4 (defined as 'severe'). The advantage to this system is that unlike the PASI, it provides an easy to interpret number that is meaningful to physicians and patients [29,32]. Studies have used this system to enable patients to perform self-assessment as a corollary to a physician's clinical assessment, thereby providing both static and dynamic measures of a patient's disease severity [33]. Concerns surrounding this system stem from the dependency on physician and patient recall, which is why static assessments are now typically the standard. Photographs have been introduced as a mechanism to fully examine changes over time when using this system [34]. The Lattice System Physician's Global Assessment provides a global psoriasis score that ranges over eight steps from clear to very severe. The investigator rates the induration, erythema and scaliness of the lesion, each on a none-to-mild, moderate or marked scale

and combines this with the percentage of BSA covered. This assessment facilitates the categorization of psoriasis into one of eight categories 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 [32], there are limitations 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 equals or 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 [35]. Lesions in mechanically sensitive areas may cause discomfort, itching or bleeding, and interfere with activities of daily living [36]. One analysis quantified the impact of psoriasis on patients with a mean PASI score of 13.0; nearly 75% of these patients reported lower self-confidence and more than 80% felt the need to hide their psoriatic lesions [37].

To address these QOL issues, many different assessments have been utilized including the EQ-5D, SF-36 and Dermatology Life Quality Index (DLQI). The EQ-5D and SF-36 are generic health status questionnaires and do not specifically relate to psoriasis or dermatology. By contrast, the DLQI has been globally included in psoriasis clinical trials as a secondary end point due to its reliability and consistency [38]. One end point is meeting a desired target score of 0 or 1 out of 30 (little to no impact on QOL), although there are also clinically established 'bands' of severity. Of note, the DLQI is now used in some countries as one measure determining the appropriateness of treatment. However, some studies focusing on the DLQI's specific use in psoriasis have cited limitations [39]. There is also a number of new patient-reported outcome measures that meet the current FDA guidance on developing patient-reported outcomes and these are starting to be used in some study settings. Other secondary scoring systems may include Nail Psoriasis Severity Index, Scalp PGA, palmar–plantar PGA and visual analog scales to assess arthritis, pruritus and/or discomfort.

End points

End points in clinical trials for moderate-to-severe psoriasis vary depending on development phase. The primary end points of a Phase I trial tend to focus on safety measurements, such as physical examination, vital signs, echocardiogram, common laboratory tests (complete blood count, chemistry, urinalysis), adverse events and tolerability assessments. Secondary end points may assess pharmacokinetics of the tested agent and clinical response in lesions. However, the main focus of a Phase I study remains safety and tolerability.

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 [40].

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% [41,42] 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 the substantial efficacy of some agents, Phase III programs 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 of database collection. This is one of the reasons that regulatory bodies typically mandate post-marketing authorization studies and registries, especially with novel therapeutic agents. The length of a psoriasis clinical trial has to be sufficient to detect not only the effectiveness of the therapy but also the potential risks. Because psoriasis is a disease easily visible on the skin, some trials have demonstrated effects as early as 2–4 weeks after their initiation. Typically, primary end points in psoriasis are measured at time points ranging from 12 to 16 weeks [9,10]. Invariably, studies continue for long periods beyond the primary end point to demonstrate remission, the length of the response and to better investigate the safety and risk profile of the therapy [9].

Study visits

Typical studies begin with a comprehensive screening visit during which a patient's medical history, physical examination and laboratory results are obtained to establish a baseline health, both overall and with respect to their disease. Based on data gathered at screening, it is determined whether a patient is suitable to undergo the study regimen according to the study protocol's inclusion and exclusion criteria. These initial assessments also allow the clinicians to evaluate treatment response during the trial, and identify if any adverse events occur. Subjects are required to washout their current psoriasis medications, topical, phototherapy, systemic and biologic agents for predetermined periods before beginning study treatment. Moreover, it should be noted that the performance of clinical study in many other conditions (e.g., rheumatoid arthritis, Crohn's disease and ulcerative colitis) permits the continuation of medications (e.g., immunosuppressants or steroids) if doses were deemed stable. This represents a major difference to the study of a new agent in psoriasis wherein both the washout period and monotherapy approach supports reduced risk of adverse drug interactions as well as confounding of data [43].

Patients selected for inclusion are re-examined at a second baseline visit to confirm eligibility and successful 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. The final visit usually consists of a full physical examination, as well as the appropriate laboratory tests and relevant assessments. The final visit closely mirrors 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 efficient data collection throughout the trial, Case Report Forms are supplied by the study sponsor for data collection across study sites and to maintain accurate records. This becomes especially important in large, multicenter trials, where it is essential to standardize data collection across all sites. The Case Report Forms ensures that the protocol is being followed precisely with no necessary tests or evaluations being skipped during any given visit.

If a study drug is promising and the benefits appear to outweigh the risks, an extension or maintenance study is often 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 this point and if well planned, the subject will be able to receive the study medication into the extension 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 support. Flyers and advertisements can also be distributed to the various facilities and posted around local hospitals 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. Mailings and telephone calls to appropriate prospective subjects, who have previously agreed to be contacted, is also an effective recruitment tool. Institutions and sponsoring pharmaceutical companies require that all telephone scripts, mailings, flyers, and additional recruitment materials be approved by an Institutional Review Board prior to distribution [102].

Once a potential subject has shown interest in the trial, it is essential to properly inform the subject about the risks and benefits of the trial and have well-trained staff available to answer all outstanding questions. This may include mention of the existence of the Data and Safety Monitoring Board for the trial, an independent group of experts that advises the trial sponsor and study investigators. The Data and Safety Monitoring Board reviews and evaluates the accumulated study data for participant safety, study conduct and progress, and can make recommendations on the continuation, modification or termination of the trial. The subject is then provided with the appropriate informed consent form

to review in the presence of the research staff before giving their consent to participate in the trial.

Limitations of psoriasis clinical trials

There are several limitations to the psoriasis clinical trial framework as outlined above. For instance, this framework cannot be readily applied to trials of topical agents for a number of reasons, but most importantly that this different population is composed of patients withmild-to-moderate disease, who are not appropriate candidates for systemic therapy. In terms of scoring systems, the PASI lacks sensitivity formild-to-moderate disease with low BSA involvement and is therefore not commonly utilized for the assessment of response to topical therapy [27,45]. Outcome measures that incorporate a global assessment of overall disease severity or improvement or focus on individual lesion improvement are more reliable [46–48]. Patients with phenotypes other than chronic plaque psoriasis, such as erythrodermic, guttate, palmar–plantar or pustular, are excluded from trials of systemic and biologic therapies, resulting in a current lack of assessment tools and treatment algorithms for these disease subtypes [14,49]. Thus, although this framework is relatively comprehensive for trials of systemic agents in psoriasis, it is not broadly applicable to all clinical trials destined to study agents that might impact psoriasis.

Conclusion & future perspective

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 other immune-mediated inflammatory disorders. Subjects with psoriasis tend to be relatively healthy, and the ability to include placebo control is advantageous to 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) tool [50]. 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 therapies in the clinic [51]. 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 also need to be suitable to evaluate for other forms of psoriasis, including erythrodermic, guttate, pustular and inverse psoriasis. The development of predictable 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 regarding 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 common, chronic, systemic inflammatory disorder that tends to manifest on the skin in people of all ethnic backgrounds. Consequently, its accessibility for measurement facilitates uncomplicated 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 immune dysregulation. 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 to study. Thus, psoriasis should be considered the pre-eminent proof-of-principle condition for any candidate therapy with a potential anti-inflammatory mode of action.

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Executive summary

- Psoriasis is a proof-of-principle condition. Clinical trials in this complex disease can be designed to be of value in basic immunology research and early therapy development for a variety of systemic immune-mediated inflammatory disorders.
- Design of clinical trials for psoriasis requires special consideration of the evaluation method for this highly visible condition.
- Psoriasis Area and Severity Index, Physician's Global Assessment and quality of life are currently used as psoriasis assessment tools in clinical trials and have validated utility.
- While limitations do exist with the available psoriasis evaluation tools, current trends focus on the use of biochemical markers to evaluate disease severity, pharmacogenomic markers to predict disease responsiveness, as well as investigation of therapeutic agents for decreased systemic inflammation and risk of associated comorbidities.

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