Original Research Article

Understanding Psoriasis Clinical Trials Landscape in India with Special Focus on Biologics

Abstract

Psoriasis is a non-communicable disease characterized by inflammation involving cutaneous T cells, dendritic cells, and keratinocytes. Release of cytokines leads to keratinocyte hyperproliferation and scaly plaques, and other manifestations of the disease including psoriatic arthritis, cardiovascular disease, and metabolic syndrome. Emollients; topical therapy with corticosteroids, vitamin D and vitamin D analogues, tar preparations, and dithranol; and phototherapy may help in mild to moderate disease, but as the disease worsens, methotrexate, ciclosporin, acitretin, apremilast (phosphodiesterase 4 inhibitor), biologics, and oral Janus Kinase or JAK inhibitors may be needed. Biologics include monoclonal antibodies that block cytokines or cytokine receptors are indicated in moderate to severe psoriasis. Several biologics are available, including tumor necrosis factor (TNF) inhibitors etanercept, adalimumab, infliximab, and certolizumab; interleukin 12/interleukin 23 inhibitor ustekinumab; interleukin 17 inhibitor secukinumab, ixekizumab and brodalumab; and interleukin 23 inhibitor guselkumab and tildrakizumab. Psoriasis disease has been a focus of clinical research worldwide, and India has also taken active part in clinical research in this area. Clinical trial registry of India shows that both indigenous medicines and allopathy drugs have been tested in clinical trials in India, including biologics such as adalimumab, etanercept, secukinumab, golimumab, ixekizumab, and ustekinumab. In this paper we wish to discuss the evolving landscape of psoriasis clinical trials in India, the evaluation and monitoring measures used, the number of psoriasis patients in India, and the average number of psoriasis patients seen in Indian dermatology clinics.

Keywords: Psoriasis; Clinical trial; Biologics; Infliximab, Adalimumab; Etanercept; Secukinumab; Golimumab; Ixekizumab; Ustekinumab

Introduction

Psoriasis is a non-communicable, chronic, pruritic, occasionally painful, disabling disease that has huge negative impact on patients' quality of life even if the lesions are localized and occupy relatively little body surface area.[1-4] The countries with highest number of adults affected with psoriasis are the United states (3.4 million), India (2.9 million), China (2.3 million), Germany (1.5 million), Brazil (1.2 million), France (1 million), and the United Kingdom (1 million).[5] Besides the impact on health, psoriasis also results in restrictions in participating in social and domestic activities.[6] The disease is marked by an immune mediated inflammation involving cutaneous T cells, dendritic cells and keratinocytes. [7-9] Cytokines are released subsequently leading to keratinocyte hyperproliferation that results in the scaly plaques. [7,8] Major cytokines involved in pathogenesis of psoriasis are interleukin (IL) including IL-2, IL-17A, IL-17F, IL-21, IL-22 and IL-23; tumor necrosis factor alpha (TNF-α), and interferon gamma (IFNγ).[2,9-13] The immune mediated inflammatory response contributes to the underlying mechanism in cardiovascular disease (including

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atherosclerosis, hypertension), metabolic syndrome, and psoriatic arthritis. [4,7,14-21] Currently, biologic agents (monoclonal antibodies and fusion proteins) that act by blocking these cytokines or cytokine receptors have shown promising results in treatment of psoriasis.[4,7] Though there has been a significant advance in treatment options, and research and trials continue to find a better method to treat, it still remains an incurable disease.[1,3,22,23]

Objectives

To evaluate the clinical trials experience in psoriasis in India, including experience with using scores or measures [like BSA (body surface area), PASI (Psoriasis Area and Severity Index), Physician's Global Assessment (PGA), Dermatology Life Quality Index (DLQI)], and approximate number of psoriasis patients in India, and patients seen per week by dermatologists in major dermatology.

Materials and Methods

An advisory board (Dermatology Scientific Expert Committee Meeting) was convened on 16th of June 2021 to discuss the clinical practice and clinical trials in psoriasis in India. The panelists were prominent dermatologists in India, including Dr. Bela Shah (Ahmedabad, Gujrat), Dr. Kiran Godse (Navi Mumbai, Maharashtra), Dr. Yogesh Marfatia (Vadodara, Gujrat), Dr. Ramesh Bhat (Mangalore, Karnataka), Dr. Davinder Parsad (Chandigarh), and Dr. Sushil Pande (Nagpur, Maharashtra). The advisory board was hosted by IQVIA India Medical & Operations team.

The psoriasis clinical research database publicly available at Clinical Trials Registry of India (CTRI) was used to identify the number of clinical trials for different treatment modalities including drugs.[24] We searched for clinical trials on psoriasis (including psoriatic arthritis) in the CTRI database, and the results are summarized in table 1.

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Table1 : Clinical Trial Registry of India (CTRI): Psoriasis Trials

IP/Therapy	Number of Trials	IP/Therapy	Number of Trials
Bath PUVA therapy	2	Propylthiouracil (tablet)	1
Topical calcipotriol	3	Isotretinoin	2
Apremilast	9	Acitretin	1
Venusia Max Cream	1	Dimethyl Fumarate (Alvogen Malta)	1
Topical steroids	3	Clobetasol propionate topical	3
Methotrexate	28	Adalimumab	5
AEB071 (Tab)- protein kinase C- inhibitor	1	AUR-101, small molecule inverse agonist of RORγ, IL 17 modulator	1
Infliximab	1	Cyclosporin A liposomal gel	3
Tazarotene 0.1% cream	1	Etanercept	2
Halobetasol propionate (0.05%) ointment	1	Secukinumab	5
HB Cream EPBF2	1	Golimumab	1
Cognitive behavioral therapy	1	Ixekizumab	1

T1h mAb	2	Ustekinumab	1
Indigenous medicines (Ayurveda, Unani, and others)	124		
Reference: Clinical Trials Registry-India. ICMR-National Institute of Medical Statistics. http://ctri.nic.in/Clinicaltrials/login.php			

The information from CTRI database, together with discussion with prominent dermatologists in India (the panelists in the dermatology advisory board) helped in understanding the landscape of psoriasis clinical trials in India. The discussions aimed to bring to the fore not only the huge potential of such trials in India, but also the major challenges to enrollment.

Results

The clinical trials registry of India (CTRI) database shows that dermatologists in India has actively taken part in clinical research in psoriasis, including psoriatic arthritis.[24] The data shown in table 1 clearly depicts that the indigenous medicines (Ayurveda, Unani, and others) dominated the number of trials conducted and registered with CTRI. This reflects the tendency of the general population as well, who tend to choose indigenous medicines fearing the side effects of allopathy practices. When the disease worsens, they turn to allopathy, as clarified by our dermatology advisory board panelists.[24] With reference to the allopathy system of practice, most of the psoriasis clinical trials registered with CTRI have evaluated methotrexate and apremilast; the registry shows Indian dermatologists have experience in psoriasis clinical trials involving biologics including infliximab, T1h mAb (T1h monoclonal antibody), adalimumab, etanercept, secukinumab, golimumab, Ixekizumab, and Ustekinumab), and protein kinase C inhibitors (table 1).[24]

Systematic review of the prevalence of psoriasis in the world was done by Parisi et al. They included 159 studies from 12 regions of the world, including central Europe, eastern Europe, central Asia, south Asia, east Asia, south-east Asia, Oceana, Latin America and the Caribbean, middle east, north Africa, and sub Saharan Africa. After analyzing the data, they concluded that there are approximately 2.9 million adult patients with psoriasis in India, 3.4 million adult psoriasis patients in USA, 2.3 million in China, and 1.5 million in Germany.[5]

Our dermatology advisory board panelists confirmed that India has a great landscape for psoriasis clinical trials. Methotrexate has been extensively evaluated, and recently there has been a rise in clinical trials to evaluate biologics in psoriasis. Most of the panelists see about 10 patients of psoriasis per week, the range being 6 to 80 patients per week, approximately 30% of these patients are new patients. There are 558 Medical colleges in India and the attached hospitals are attended by many cases.[25] The population is huge, with huge diversity, making it possible to enroll patients with diverse racial and ethnic backgrounds. The panelists in our dermatology advisory board confirmed that they regularly use scoring tools including BSA, DLQI, PASI, Nail psoriasis severity index, and psoriasis epidemiological screening tool (PEST) in their clinical practice and clinical research. The panelists mentioned that their experience is robust in BSA, DLQI, PASI, Nail psoriasis severity index, and psoriasis epidemiological screening tool.

The key findings in the discussion are given below:

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1. Indigenous medicines for psoriasis are popular in India, but when the severity of disease increases, the patients are relatively more compliant to allopathy treatment.
2. The cost of medicines can be a deterrent.
3. Patients and physicians are open to clinical trials, including biologics.
4. The institutional ethics committees (IEC) in India evaluate the methodology of clinical trials in detail. Generally, IECs are concerned if there is a placebo arm in such clinical trials, especially in case of systemic therapies, as using a placebo arm means some patients will not receive therapy making it difficult to accept the proposal ethically.
5. Training support to both healthcare professionals and patients- especially regarding use of biologics, dedicated staff to ensure compliance of the patients and for monitoring, option of open label extension, and other supportive measures like patient's e-diary (to be filled by patient, either with or without healthcare worker's guidance) may help in increasing enrollment and compliance in clinical trials.
6. Indian dermatologists have robust experience with BSA, DLQI, PASI, nail psoriasis severity index, and psoriasis epidemiological screening tool (PEST).
7. Indigenous medicines (Ayurveda, Unani, and others) dominated the number of trials conducted and registered with CTRI. This reflects the tendency of the general population as well, who tend to choose indigenous medicines fearing the side effects of allopathy practices. When the disease worsens, they turn to allopathy and are usually compliant to the treatment as confirmed by our dermatology advisory board panelists.
8. Indian dermatologists have a good experience in psoriasis clinical trials involving biologics including infliximab, T1h mAb (T1h monoclonal antibody), adalimumab, etanercept, secukinumab, golimumab, Ixekizumab, and Ustekinumab), and protein kinase C inhibitors.

Discussion

The prevalence of psoriasis varies in countries and different geographical regions, the range being 0.09% to 11.4%.[1] In a systemic review and meta-analysis, Rosa Parisi et al estimated that the prevalence of psoriasis was 0.11% in east Asia to 1.58% in Australasia and 1.52% in western Europe.[5] Psoriasis is most common in 50-69 years age group, though it can occur at any age.[2] Some studies suggested that average age of onset of psoriasis was 33 years, and 75% of the psoriasis cases were seen in patients below 46 years of age, other studies identified that onset of psoriasis followed a bimodal pattern of distribution, with one peak between 16 and 22 years of age, and another between 57 and 60 years.[1]

Looking at the country specific percentage, physician diagnosed lifetime prevalence of psoriasis is estimated to be highest in Australia (2.38%), Norway (2.36%), Israel (2.28%), Denmark (2.26%), Romania (2.24%), Germany (2.22%), Sweden (2.10%), Poland (2.06%), and Italy (2.00%).[5] The prevalence was low in east Asia and Taiwan (lowest).[5] Now, when we want to estimate total number of patients affected in a country, the population of the country has to be taken into account. The most populous country is China, with 1.44 billion people.[26] Population of India is 1.39 billion, the second most populous country in the world.[26] The estimates in the systemic review and meta-analysis by Rosa Parisi et al shows that the countries with highest number of adults affected with psoriasis were the United states (US) (3.4 million), India (2.9 million), China (2.3 million), Germany (1.5 million), Brazil (1.2 million), France (1 million), and the United Kingdom (UK)(1 million).[5]

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Some studies have shown that the global prevalence of psoriasis does not differ between males and females, other studies have shown that males are more commonly affected than females.[1,5]

Common types of psoriasis include psoriasis vulgaris, intertriginous psoriasis, guttate psoriasis, pustular psoriasis, and erythrodermic psoriasis.[1] The most common form of psoriasis is psoriasis vulgaris (plaque psoriasis) affecting 58% to 97% of all psoriasis patients.[1] Prevalence of nail psoriasis ranges between 4.2% and 69%- nail changes can be seen in approximately 50% of psoriasis patients, and are more common in those who have psoriatic arthritis.[1,27] Psoriatic arthritis occurs in 25% to 30% of all psoriasis cases.[4,7]

Psoriasis has a huge impact on the quality of life. [6] A study by Rajan Pichaimuthu et al in Indian patients revealed that 28% of psoriasis patients participated minimally in domestic and social life. [6] The investigators found that there was an extreme participation restriction in 2.7% of psoriasis patients. Prevalence of diffidence, difficulties in work, education, and employment, and in their social life.[6] Another study by Neelu Sharma et al in Indian patients found that 53.3% of psoriasis patients had psychiatry morbidity on being evaluated with General Health Questionnaire (GHQ-H), with 23.3% of psoriasis patient suffering from depression, and 56.6% with sleep disturbances.[28] These problems in psoriasis patients have been identified in other studies worldwide.[6,29-31]

Associated Diseases

Patients with psoriasis may have associated comorbidities including atherosclerosis, vascular inflammation, atrial fibrillation, stroke, Crohn's disease, depression, erectile dysfunction, renal disease, and metabolic syndrome including diabetes mellitus, hypertension, and dyslipidemia.[1,4,7,23,27,32, 33]

Weight gain, obesity and tobacco smoking are risk factors for psoriasis.[1,7,27,33] N Asokan et al investigated association between smoking and alcohol with severity of psoriasis. They enrolled 338 psoriasis patients in India, (148 smokers, 173 with history of consuming alcohol). They found that smoking, and not alcohol, was associated with increased severity of psoriasis.[34]

Psoriasis has been shown to be an independent risk factor for non-alcoholic fatty liver disease.[1,7,27] Sunil K Kothiwala et al investigated prevalence of metabolic syndrome and cardiovascular morbidity in patients with plaque psoriasis. They found that prevalence of metabolic syndrome was higher (39.3%) in plaque psoriasis (controls: 17.1%). Prevalence of hypertension, abdominal obesity and diabetes was also found to be higher in psoriasis patients than controls in this study.[35] More studies are required in this area to confirm the association of comorbidities and psoriasis, and any causality relationship.[1,27,35]

Tools for Assessment

Several tools are available and are used both in clinical practice and clinical research in psoriasis, including HRQoL (health-related quality of life measure), PASI, BSA, Nail psoriasis severity index, DLQI or Children's Dermatology Life Quality Index (CDLQI) as appropriate, and PGA. [1,4,9,27,36-38] For psoriatic arthritis, tools used by clinical researchers and dermatologists/rheumatologists are Toronto PsA Screen (ToPAS), the Psoriasis Arthritis Screening and Evaluation Questionnaire (PASE), and PEST.[1,4,9,27] On being asked, the panelists in our dermatology advisory board confirmed that they regularly use these measures in their clinical practice and clinical research, especially the BSA, DLQI, PASI, Nail psoriasis severity index, and PEST.

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Treatment

Treatment options available for psoriasis are topical therapy including vitamin D3 analogues, corticosteroids, anthralin/dithranol, topical retinoids, tacrolimus; phototherapy; and systemic therapy including methotrexate, ciclosporin, acitretin, apremilast (phosphodiesterase 4 inhibitor), biologics, and oral small molecules (Janus Kinase or JAK inhibitors).[1,3,7,39-41,42] As per National Institute for health and care excellence (NICE) guidelines (UK), the lines of therapies are as follows:

1. **First line:** traditional topical therapies (corticosteroids, vitamin D and vitamin D analogues, dithranol, and tar preparations).[27]
2. **Second line:** phototherapy (broad-band or narrow-band ultraviolet B-light; psoralen plus UVA light or PUVA) and non-biological systemic agents including ciclosporin, methotrexate and acitretin.[27]
3. **Third line:** systemic biological agents including the monoclonal antibodies TNF (tumor necrosis factor) antagonists adalimumab, etanercept and infliximab, and the monoclonal antibody ustekinumab, ixekizumab and secukinumab.[27]

Topical therapy and phototherapy may be adequate for treatment of mild to moderate psoriasis, but when the severity increases to moderate to severe, topical therapy alone or in combination with phototherapy may not be sufficient.[7,27] Non-biologic systemic agent tofacitinib, an oral Janus kinase (JAK) inhibitor has shown promising results in psoriasis treatment, but it has not been approved yet (though it is an approved therapy for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis.[39,41,43-46] Biologic agents, either as monotherapy or in combination with other agents, may be required in moderate to severe cases.[7,27] The biologics include the monoclonal antibodies including tumor necrosis factor (TNF) inhibitors etanercept, adalimumab, infliximab, and certolizumab; IL-12/IL-23 inhibitor ustekinumab; IL-17 inhibitor secukinumab, ixekizumab and brodalumab; and IL-23 inhibitor guselkumab and tildrakizumab (table 2).[4,7,13,47-51]

Table 2: Biologics for Treatment of Psoriasis
Tumor Necrosis Factor (TNF) Inhibitors
Etanercept
Adalimumab
Infliximab
Certolizumab
Interleukin 12 (IL-12)/Interleukin 23 (IL-23) Inhibitor
Ustekinumab
Interleukin 17 inhibitors
Secukinumab
Ixekizumab
Brodalumab
Interleukin 23 inhibitors
Guselkumab
Tildrakizumab

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Reference: Menter A, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019 Apr;80(4):1029-1072.

Dermatologists and clinical researchers in India have a good experience of clinical research in psoriasis and psoriatic arthritis, including use of biologics for treatment of psoriasis and psoriatic arthritis, as shown in the psoriasis studies database in CTRI, case reports and original studies published by investigators focusing on Indian population, and discussions by dermatologists in our dermatology advisory board.[24,42,52-56]

This panel discussion, data of CTRI website, and review of literature emphasizes the point that India has an evolving clinical research arena, with good experience of using biologics for psoriasis in clinical practice and clinical research, good experience of using the tools like BSA, PASI, and PEST scores, and could be a dependable clinical trials region in psoriasis therapeutic area including use of biologics. Some challenges still persist, including the cost of the biologics hindering continued use of these valuable medicines after the trial is over, prevailing beliefs and tendency of Indian people to use indigenous medicines, and ensuring adequate training, dedicated personnel, and measures to improve compliance using reminders and e-diary. These factors need to be carefully considered while designing the risk assessment and mitigation plan in order to have a successful clinical trial involving biologics for treatment of psoriasis in India.

Conclusion

Psoriasis is associated with inflammation involving cutaneous T cells, dendritic cells and keratinocytes. The inflammatory cells release cytokines that lead to keratinocyte hyperproliferation and scaly plaques, psoriatic arthritis, cardiovascular disease, and metabolic syndrome. Topical therapy with emollients; topical corticosteroids, vitamin D and vitamin D analogues, tar preparations, and dithranol; and phototherapy are used in mild to moderate psoriasis. Moderate to severe disease necessitates use of methotrexate, ciclosporin, acitretin, apremilast (phosphodiesterase 4 inhibitor), biologics, and oral Janus Kinase or JAK inhibitors may be needed. Biologics include monoclonal antibodies that block cytokines or cytokine receptors are indicated in moderate to severe psoriasis. Several biologics are available, including tumor necrosis factor (TNF) inhibitors etanercept, adalimumab, infliximab, and certolizumab; interleukin 12/interleukin 23 inhibitor ustekinumab; interleukin 17 inhibitor secukinumab, ixekizumab and brodalumab; and interleukin 23 inhibitor guselkumab and tildrakizumab. Biologics, either as monotherapy or in combination with other treatment options, is gradually gaining ground in treatment of moderate to severe psoriasis. Clinical trial registry of India shows that both indigenous medicines and allopathy drugs have been tested in clinical trials in India, including biologics such as adalimumab, etanercept, secukinumab, golimumab, ixekizumab, and ustekinumab. Rosa Parisi et al estimated in their systemic review and meta-analysis that India is among the countries with highest number of adults affected with psoriasis (2.9 million patients). The panelists in our advisory board said that the number of psoriasis patients they see in their clinics are huge, with average being 10 psoriasis patients per week, with 30% of these being new patients. Indian dermatologists have a good experience in psoriasis clinical trials, including biologics, as evident from the CTRI database and panelists' discussion. Based on these (CTRI database, panelists'

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inputs, and data from published epidemiology studies), the authors conclude that India holds a good promise in recruiting a good number of psoriasis patients for clinical trials.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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