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REVIEW

Patient considerations and targeted therapies in the management of psoriasis in Chinese patients: role of ustekinumab

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Abstract: Psoriasis is an immune-mediated disease affecting approximately 0.1% to 0.5% of the population in the People's Republic of China. Multiple therapeutic options are available for the treatment of moderate to severe psoriasis although they all have their respective disadvantages. The application of biological agents has brought significant efficacy in psoriasis treatment. Ustekinumab, a human monoclonal antibody targeting the interleukin-12/23 pathway, shows its superiority in efficacy, long duration of drug action, and good tolerance in patients. Phase III clinical trials of ustekinumab have been completed in Mainland China, and the drug is available in Taiwan and Hong Kong. Meanwhile, its long-term safety and efficacy merit further investigation.

Keywords: psoriasis, biologics, ustekinumab, Chinese patients

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Introduction

Psoriasis is a chronic, immune-mediated disease affecting 2% to 3% of the population worldwide.[1] The incidence and prevalence rates vary greatly between people of different ethnic backgrounds and geographic regions. Psoriasis is most common in Caucasians, and the incidence rate in Caucasians is estimated to be 60/100,000 person-years.[2] Studies on psoriasis showed that the prevalence rate in adults varied from 0.91% (US) to 8.5% (Norway), and incidence rates in adults varied from 78.9/100,000 person-years (US) to 230/100,000 person-years (Italy).[3]

Chinese people have lower prevalence rates compared to Caucasians. A large cross-sectional study in 1984 collected epidemiological data from 24 provinces in Mainland China and found that psoriasis affected only 0.123% of the general population.[4] From then on, no nationwide epidemiological survey has been conducted. Instead, some epidemiological data from studies in local areas have been made available. A community-based survey conducted in six cities from six provinces in the north and west of the People's Republic of China in 2010 obtained a prevalence rate of psoriasis of 0.47%.[5] Another epidemiological survey in 2013 of 18 cities or counties in Hainan Province, the most southern part of the People's Republic of China, showed that the prevalence rate of psoriasis was 0.149%.[6] A cross-sectional study in Jiaozuo City of central China in 2011 obtained a prevalence rate for psoriasis of 0.79%.[7] The prevalence rate of psoriasis was 0.235% in Taiwan in 2006.[8] All of these studies had geographical limitations which could not reflect the overall situation in the People's Republic of China. Nevertheless, they showed a current increase in the prevalence rate of psoriasis compared to that of more than 20 years ago, and the prevalence rate was higher in the northwest part of the People's Republic of China than in the southern region. Due to the large population

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of the People's Republic of China, there are a considerable number of psoriasis patients demanding adequate attention and medical services.

Psoriasis and therapeutic options

Psoriasis

Psoriasis vulgaris is characterized by erythematous, scaly plaques, which are commonly seen on the elbows, knees, lower back, and umbilical area, although many patients have plaques on sensitive areas that cause substantial discomfort such as the scalp, face, hands, feet, and genitalia. Approximately 25% of individuals with psoriasis develop moderate to severe disease with widely disseminated lesions.[2,9] Psoriasis is also associated with multiple comorbidities, including psoriatic arthritis (PsA), depression, cardiovascular disease, obesity, diabetes, metabolic syndrome, and Crohn's disease.[10] As a result, patients with psoriasis have a significantly impaired quality of life (QoL), and satisfactory therapeutic approaches are required.

PsA has been defined as a unique inflammatory arthritis associated with psoriasis which typically presents as an oligoarticular and mild disease.[11] Among patients with psoriasis, 6%–42% of Caucasians were reported to have PsA, but figures were lower from Asian countries (1%–9%).[12] The prevalence rate of PsA among patients with psoriasis in the People's Republic of China was 5.8% according to a large cross-sectional observational study conducted in 2010. Compared with patients without PsA, patients with PsA had more severe skin disease (mean Psoriasis Area and Severity Index[13] [PASI] 9.7 versus 6.0), higher frequency of nail changes (46.4% versus 21.0%), and scalp involvement (90.2% versus 76.4%).[14]

Therapeutic options in the People's Republic of China

Topical agents are commonly used in mild psoriasis, including topical corticosteroids, dithranol, tar-oil, vitamin D derivatives, topical retinoids, and calcineurin inhibitors.[15] Besides those topical agents, multiple therapeutic options in the People's Republic of China can be chosen for the treatment of moderate to severe plaque psoriasis. However, the unmet need remains significant for a safer and more effective, convenient, and cost-effective ratio systemic therapy. Methotrexate, cyclosporine, sulfasalazine, and azathioprine can offer effective control in many cases, but organ toxicity should be taken into account in long-term use.[15] Acitretin has less risk of specific organ toxic effects, but it is teratogenic and therefore inappropriate for many female patients of childbearing age. These drugs also have the potential for interactions with other drugs, which may limit their use in some patients due to safety concern.[16]

The therapy of psoralen plus ultraviolet A exposure, although effective, is inconvenient and infrequently used in the People's Republic of China. Narrow band ultraviolet B, 308 nm excimer light, and high-energy red light is also used to treat psoriasis. These physical therapies are all associated with an increased risk of skin malignancies and photodamage.[16,17]

Traditional Chinese medicine (TCM) such as *Tripterygium wilfordii*, *Tripterygium hypoglaucum*, and so on has been used for psoriasis treatment for decades in the People's Republic of China. Integrated therapy of both TCM and Western medicine is also widely accepted by Chinese doctors.[15] Unreasonable use of TCM can lead to treatment failure or even toxic effects. The efficacy and safety of TCM requires more observation and study according to evidence based medicine.

Biological agents

Biological therapies have revolutionized moderate to severe psoriasis treatment. Tumor necrosis factor (TNF)-α is one of the established targets for biological therapies that plays a significant role in psoriasis pathogenesis. To date, anti-TNF-α agents have been used to treat over three million patients worldwide for many immune-mediated diseases.[18] The widely used anti-TNF-α agents for psoriasis currently are adalimumab, etanercept, and infliximab.

In Mainland China, etanercept was the first biologic introduced into the People's Republic of China and approved by China's Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, ankylosing spondylitis, and moderate to severe plaque psoriasis in 2005. It also shows efficacy in the treatment of PsA.[19] Infliximab was approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, moderate to severe active Crohn's disease, and fistulizing Crohn's disease by China's FDA in 2006. Infliximab's indication of moderate to severe plaque psoriasis was then approved by China's FDA in 2013.[19] Another anti-TNF-α agent, adalimumab is still in Phase III clinical trial. We prefer these biological agents in our clinical practice when poor effects are achieved by other therapies, especially for severe plaque psoriasis and PsA.

Ustekinumab, a human monoclonal antibody targeting the interleukin (IL)-12/23 and T helper (Th)17 pathway, has been approved for marketing in Canada as early as in

2008 for the treatment of adult moderate to severe plaque psoriasis.[20] Phase III clinical trials of ustekinumab in Mainland China were completed last year, and the drug will be available on the market soon. However, in Taiwan and Hong Kong, etanercept, adalimumab, and ustekinumab can be prescribed.

There are many other biological agents. Briakinumab, another human monoclonal antibody targeting the shared p40 subunit of IL-12 and IL-23, was found to be related to a small number of major adverse cardiovascular events. Therefore, Phase III studies and further development of the medication were forced to be discontinued in January 2011.[18] Brodalumab is a human monoclonal immunoglobulin (Ig) G2 antibody that targets the IL-17 pathway through binding of the IL-17A receptor and is now being investigated in Phase III studies.[18] Ixekizumab is a human monoclonal IgG4 antibody, and secukinumab is a human monoclonal IgG1 isotype antibody. They both bind the IL-17A cytokine and are in Phase II studies now.[18] MK-3222, guselkumab, and BI655066 are all anti-IL-23p19 agents. Phase III studies on MK-3222 are currently underway.[18] Other biological agents, such as AbGn-168H, BT-061, ASKP1240, etc, are all in early stages of studies.[18]

Psoriasis immunopathogenesis and ustekinumab

Psoriasis immunopathogenesis

Activation of aberrant immune-mediated inflammatory responses contribute to psoriasis pathogenesis.[21] The cell types identified within psoriatic plaques include keratinocytes, dendritic cells, monocytes, macrophages, and T and B lymphocytes. In a psoriatic plaque, increased expression of immune-related proteins synthesized by keratinocytes is observed, such as intercellular adhesion molecule 1, CD40, and human leukocyte antigen-DR.[21] There is a rise in the infiltration and expansion of several types of leukocytes and in the number of inflammatory dendritic cells and plasmacytoid dendritic cells.[21] Keratinocytes also increase leukocyte trafficking into diseased tissue by greater synthesis of S100 proteins in psoriasis.[22]

Some other inflammatory cytokines and pathways have been studied as therapeutic targets. In the late 1990s, analysis of human psoriatic plaque tissue and animal models suggested that IL-12 was associated with psoriasis pathophysiology.[23,24] In fact, IL-12 is one of the pivotal cytokines in pathogenesis of psoriasis.[25] The expression of another cytokine, IL-23, is also found to be significantly increased in the psoriatic epidermis.[26,27] IL-23 messenger RNA expression in lesional skin of psoriatic patients is significantly higher than that of healthy skin in the same patients.[27]

IL-12 and IL-23 are both heterodimeric proteins having the same disulfide-linked, glycosylated subunit p40. IL-12 consists of p35 and p40 while IL-23 consists of p19 and p40.[28]

Numerous studies also suggested that IL-12 and IL-23 may play a central role in psoriasis pathogenesis. Polymorphisms of genes that encode either the shared p40 subunit or one of the IL-23 receptor (IL-23R) complex components are linked to psoriasis.[29–32] An uncommon IL-23R coding variant has been shown to confer protection against psoriasis.[33]

A heterodimeric receptor complex consisting of IL-12 receptor (IL-12R)β1 and IL-12Rβ2 chains is expressed on the surface of T cells or natural killer cells. The p40 subunit binds to the IL-12Rβ1 chain, whereas IL-12p35 association with IL-12Rβ2 confers intracellular signaling.[34]

Mechanism of ustekinumab

Ustekinumab binds to the p40 subunit of IL-12 and of IL-23, preventing their interaction with the cell surface IL-12Rβ1 receptor, subsequently inhibiting IL-12- and IL-23-mediated cell signaling, activation, and cytokine production.[20,28] Through isothermal titration calorimetry analysis, ustekinumab was shown to bind IL-12 and IL-23 equally. However, ustekinumab cannot bind to endogenous IL-12 or IL-23 that is already bound to receptor complexes. Furthermore, ustekinumab did not bind to structurally related proteins or rodent IL-12/23. Overall, these studies determined the precise specificity and molecular interactions between ustekinumab and IL-12/23 p40.[28]

Efficacy, safety, and tolerability of ustekinumab

Efficacy of ustekinumab

Ustekinumab's safety and efficacy were assessed in large Phase III trials. Two Phase III trials, PHOENIX 1 and PHOENIX 2, have demonstrated that ustekinumab is highly effective in ameliorating psoriatic plaques pruritus and nail psoriasis.[35,36] Within 12 weeks of initiating ustekinumab treatment (45 mg/kg or 90 mg/kg at weeks 0 and 4), more than two-thirds of patients experienced more than 75% reduction in the PASI (PASI 75) score. Maximum efficacy was achieved at approximately 24 weeks after initiation of therapy, with approximately 75% of ustekinumab treated patients achieving a PASI 75 response. Similar response patterns were observed for the proportions of patients with a Physician's Global Assessment[37] score of 0 or 1, PASI 90 response, and/or PASI 50 response.[35,36,38]

Because of its long half-life, ustekinumab yields a sustained, high level clinical response in approximately 80% of responding patients with convenient maintenance dosing of every 12 weeks. As clinical response to ustekinumab is associated with serum ustekinumab concentrations, 45 mg is employed for patients weighing ≤100 kg, and 90 mg is recommended for patients weighing >100 kg.[35,36]

In the ACCEPT Phase III trial, ustekinumab's safety and efficacy were compared with those of etanercept. The results demonstrated the superior efficacy at week 12 of ustekinumab at 45 mg and 90 mg when administered at weeks 0 and 4 in patients with moderate to severe psoriasis versus high-dose etanercept (50 mg) when administered twice weekly for 12 weeks. In addition, nearly one-half of patients who had not responded to etanercept subsequently responded to ustekinumab.[39,40]

Ustekinumab has also been evaluated in Asian patients, particularly in Taiwanese and Korean patients with moderate to severe psoriasis. One hundred and twenty-one patients with moderate to severe psoriasis were involved in this 36-week, multicenter, double-blind, placebo-controlled study. These patients were randomized (1:1) to receive subcutaneous injections of ustekinumab 45 mg at weeks 0, 4, and 16 or placebo at weeks 0 and 4 and ustekinumab 45 mg at weeks 12 and 16. At week 12, the proportion of patients achieving PASI 75 was 67.2% and 5.0% in the ustekinumab 45 mg and placebo groups, respectively ($P<0.001$). Physician's Global Assessment of "cleared" or "minimal" was achieved by 70.5% (ustekinumab) and 8.3% (placebo; $P<0.001$), and median Dermatology Life Quality Index (DLQI)[41] changes were −11.0 and 0.0, respectively ($P<0.001$). Efficacy was maintained through week 28 in ustekinumab-treated patients. The results showed good efficacy for the treatment of subcutaneous ustekinumab 45 mg.[42]

The safety and efficacy profile of ustekinumab in psoriasis patients in Mainland China is not available although Phase III trials were completed there in 2013. The final results have not yet been released publicly as of the writing of this review.

Clinical trials to investigate the efficacy of ustekinumab in the treatment of other inflammatory disorders, including PsA, have been conducted since 2009.[43] Phase II and Phase III studies showed significant efficacy of ustekinumab in the treatment of PsA. In Phase II studies conducted at 24 sites in North America and Europe in 2009, ustekinumab significantly reduced signs and symptoms of PsA and diminished skin lesions compared with placebo.[44] The 1-year results of the Phase III, multicenter, double-blind, placebo-controlled PSUMMIT 1 trial also showed both a good safety profile and significant efficacy for ustekinumab in the treatment of active PsA compared with placebo.[45] It might offer an alternative therapeutic mechanism of action to approved biological treatments.

Safety and tolerability of ustekinumab

Ustekinumab was generally well tolerated according to the results of the Phase III psoriasis clinical trials abroad. Rates and types of adverse events (AEs), serious AEs, AEs leading to treatment discontinuation, and laboratory abnormalities were generally comparable among patients receiving placebo, ustekinumab 45 mg and 90 mg during the 12-week placebo-controlled phases of PHOENIX 1 and 2. Dose-response relationships for safety events were not apparent. Immunogenicity rates were low, with approximately 5% of patients developing anti-ustekinumab antibodies. Drug administration was also well tolerated, with approximately 1% of injections having an associated injection site reaction.[35,36]

The treatment of ustekinumab for Asian patients was proved to be safe as well. In the multicenter, double-blind, placebo-controlled study conducted in Taiwanese and Korean patients,[42] AE profiles at week 12 were similar between the ustekinumab and placebo groups: 65.6% and 70.0%, respectively, and there was at least one reported AE. Through week 36, no disproportionate increase in AEs was observed, with the exception of abnormal hepatic function, which was related to concomitant isoniazid (INH) treatment for latent tuberculosis. Injection-site reactions were rare and mild. No deaths, malignancies, or cardiovascular events were reported, showing a favorable benefit/risk profile.[42]

Hepatitis B or C

The People's Republic of China has one of the world's highest rates of hepatitis B virus (HBV) infection. A nationwide HBV serosurvey conducted in 2006 showed that 7.2% of the Chinese population ranging in age from 1 to 59 years old were hepatitis B surface antigen (HBsAg) carriers.[46] An estimated 93 million people in the People's Republic of China are infected with HBV.

Chronic hepatitis B reactivation has been observed in patients receiving anti-TNF-α therapies.[18,47] Thus, anti-TNF-α agents are currently considered to be relatively contraindicated in psoriatic patients with HBV infection, based on the American Academy of Dermatology Guidelines,[48] and are not recommended by the British Association of Dermatology.[49]

Ustekinumab has no formal recommendations for screening on its package insert regarding viral hepatitis.[50]

A case of HBV reactivation during therapy with ustekinumab for psoriasis has been reported.[51] A cohort study in Taiwan evaluated the safety profile of ustekinumab in the treatment of 18 Chinese patients with psoriasis who had concomitant hepatitis B or hepatitis C. Their results showed that among eleven patients positive for HBsAg, two out of the seven (29%) patients who did not receive antiviral prophylaxis exhibited HBV reactivation during ustekinumab treatment. No viral reactivation was observed in the three occult HBV-infected patients (HBsAg-negative/hepatitis B core antibody-positive patients).[52] Antiviral prophylaxis appears to minimize the risk of viral reactivation in patients with concurrent psoriasis and HBV infection.

With regard to hepatitis C, a Phase II randomized, placebo-controlled trial has concluded that etanercept improves viral clearance rates.[53] Another retrospective, multicenter study recruited 20 patients with psoriasis and concurrent hepatitis C virus (HCV) infection who had received at least one biologic agent (three for ustekinumab). Except for one patient treated with etanercept, all other patients with HCV infection did not exhibit increases in their viral load or serum liver tests.[54]

It is widely accepted that all candidates for ustekinumab therapy should undergo screening for HBV and HCV infection and close monitoring for viral load.[18,55] However, it is not clear in which situation HBV and HCV will become an absolute contraindication, and further study in the Chinese population is needed to resolve this issue.

Tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. The incidence of TB varies worldwide, with the highest in South-East Asia (35%), Africa (30%), and Western Pacific regions (21%).[56] The most recent national epidemiological sampling survey in Mainland China was organized in 2000 involving 365,097 subjects. The results showed that the prevalence of active pulmonary TB was 0.367%, the prevalence of smear positive pulmonary TB was 0.122%, and the prevalence of bacteriological positive pulmonary TB was 0.16%.[57] A recent study reported a total of 465,960 cases of TB between January 2004 and December 2011 in Hubei, only one province in the People's Republic of China. The incidence rate was approximately 0.1%.[58] TB still remains a serious health issue in the People's Republic of China.

In order to know the influence of ustekinumab therapy on the psoriasis patients with TB, data from 3,177 psoriasis patients were analyzed across five Phase III trials of ustekinumab (45 mg or 90 mg) conducted in North America, Europe, and Asia. Of 2,898 non-Asian patients, 101 (3.5%) and 66/279 (23.7%) Asian patients were newly identified with latent TB infection (LTBI), and all were treated with INH. No cases of LTBI reactivation were observed in patients receiving concomitant INH prophylaxis during ustekinumab therapy.[56] A case of latent TB reactivation was reported in a patient treated with ustekinumab without concomitant INH chemoprophylaxis in the PEARL trial.[59] Thus, some clinicians recommended a tuberculin skin test or QuantiFERON-TB gold test (Quest Diagnostics, Madison, NJ, USA) should be done as necessary prophylaxis before use of ustekinumab and INH.[56]

The Phase III trial for ustekinumab conducted in Mainland China excluded patients with active pulmonary TB. Those patients with LTBI were all given the combination therapy of INH and rifampicin according to the clinical trial protocol. Even patients only having strong positive results for the tuberculin skin test, without any other positive evidences, were given anti-TB treatment.

Besides the tuberculin skin test, fluoroscopy, sputum smear, sputum culture, and the QuantiFERON-TB gold test, T-spot is also a specific and sensitive diagnostic method, which can only be used in a small number of hospitals and laboratories in the People's Republic of China. It is necessary to assist hospitals in implementing the use of these highly specific and sensitive diagnostic tests and to find more convenient, faster, and more cost-efficient tests with which to screen for TB before commencing biological therapies.

Other special circumstances

PsA is also an indication for biological therapy. In September 2013, ustekinumab was approved by the US FDA and the European Medicines Agency for the treatment of PsA. Ustekinumab also showed efficacy in the treatment of a series of patients with palmoplantar psoriasis and nail psoriasis.[60,61] Evidence of its effect on scalp psoriasis remains sparse.

For pregnant or postpartum patients with psoriasis, all biologics currently approved for plaque psoriasis are listed as pregnancy category B by the US FDA.[48] According to the manufacturer's guidelines for ustekinumab, women should discontinue biologics for 15 weeks before conceiving.[49,62]

Recent evidence has provided a direct link between anti-TNF-α therapy and an increased risk of skin cancer.[63] Ustekinumab, functioning through a different pharmacological mechanism, might not pose this risk, as no similar findings regarding skin cancer have been reported so far, but more observation is required to assess safety.

Quality of life and patient satisfaction

The impact of ustekinumab therapy on QoL was studied. The PHOENIX 1 and PHOENIX 2 trials both studied the impact of ustekinumab therapy on QoL, and showed that symptoms of anxiety, depression, and impaired QoL can be markedly improved with effective treatment. In PHOENIX 1, mean DLQI was >10 in all patient groups pretreatment. Normalization of DLQI (defined as DLQI <1) was observed in 53.1% (n=135), 52.4% (n=31), and 6.0% (n=15) at week 12 in the ustekinumab 45 mg, ustekinumab 90 mg, and placebo groups, respectively. A similar trend was observed for Short Form (36) Health Survey[64] scores. The impact on QoL was sustained throughout the observation period.[35,36,65]

The improvements in QoL for psoriasis patients in Taiwan were observed after treatment with ustekinumab.[66] The results of the Phase III trial in Mainland China have not yet been published.

Pharmacoeconomics of ustekinumab

Multiple treatments are optional for psoriasis therapy, and the costs vary widely. The total annual costs of methotrexate therapy (15 mg/week), cyclosporine therapy (400 mg/day), and acitretin (25 mg/day) are approximately $1,330, $10,021, and $21,736 US dollars, respectively. Ustekinumab (45 mg every 3 months), adalimumab (40 mg every other week), and etanercept (50 mg weekly) costs about $22,657, $24,049, and $24,503 US dollars a year, respectively.[67] In Mainland China, similar price differences exist between biological therapies and conventional nonbiological therapies. Although more expensive, biological agents are superior to conventional nonbiological therapies in efficacy and safety. With their widespread use and reduction of their prices in the future, the cost-effective benefits of biological agents will become increasingly obvious.

Though the People's Republic of China's economy has made rapid progress, there are still some issues to be solved, such as huge income disparity and imbalance in regional economic development. The People's Republic of China's medical care system is very different from that of other developed countries, in that some patients do not have medical insurance, and many medications and treatments are not covered by medical insurance. Even among patients having medical insurance, the reimbursement policies may vary.

All biological agents are not covered by the Chinese national medicare system in Mainland China, and their cost places an economic burden on most psoriasis patients. As the People's Republic of China's economy continues to thrive and the national medicare system continues to improve, more and more patients will receive better medical services. The policy mandating everyone in Mainland China purchase basic medical insurance will be implemented next year, and as biological agents will be included as an insured category in the future, more psoriasis patients will benefit through access to these biologics.

Conclusion

The People's Republic of China has a large number of psoriasis patients and treatment has become an increasingly serious issue in public health. Biological agents for psoriasis therapy were introduced into Mainland China only in recent years, but they have already showed their superiority compared to the nonbiological therapies. Ustekinumab is a new biological agent for the treatment of moderate to severe psoriasis, demonstrating the advantages of greater efficacy, long duration of drug action, and good patient tolerance. Along with its scheduled launch in the People's Republic of China in 2014, ustekinumab will provide superior efficacy and safety benefits for psoriasis patients.

Disclosure

The authors report no conflicts of interest in this work.

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