Exploring Priority Research Areas in Psoriasis and Psoriatic Arthritis from Dermatologists' Perspective: A Report from the GRAPPA 2011 Annual Meeting

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ABSTRACT. At the 2011 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in Naples, Italy, the GRAPPA dermatology members led discussions on priority research areas in psoriasis and psoriatic arthritis (PsA). These discussions centered on 3 primary areas: evaluation of PsA screening tools, updates on psoriasis comorbidities, and new developments in genetics and comparative effectiveness research. Introductory presentations were followed by engaging panel discussions and audience interaction. The members agreed that screening tools are highly valuable in early detection of PsA among dermatology patients and that efforts are necessary to develop tools suitable for adoption in clinical practice. Members also agreed that a collaborative investigation to evaluate the effect of psoriasis treatments on cardiovascular comorbidities would be highly informative. Finally, the members supported continued efforts to explore the genetic basis of psoriasis and more studies focused on comparative effectiveness of existing treatments. (J Rheumatol 2012;39:2204–10; doi:10.3899/jrheum.120825)

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Detecting Psoriatic Arthritis in the Dermatology Population: Development, Validation, and Evaluation of Screening Instruments

Overview of psoriatic arthritis screening tools. Early detection of psoriatic arthritis (PsA) is an important aspect of caring for patients with psoriasis. Because about 70%–80% of patients with PsA develop joint symptoms after the onset of skin manifestations of psoriasis, detection of PsA in dermatology clinics can facilitate timely diagnosis and treatment of PsA. However, the ability to accurately identify patients with PsA varies depending on clinician experience. The PsA classification criteria proposed by Moll and Wright and the CASPAR (ClASsification of Psoriatic ARthritis) criteria have been applied widely to diagnose patients with PsA[1]. While these and other classification criteria have been shown to have excellent sensitivity and specificity in selected patient populations[2,3,4], the CASPAR criteria in particular require identification of inflammatory musculoskeletal disease, which can be challenging for a non-rheumatologist. Therefore, screening questionnaires are necessary to identify patients with a greater likelihood of having PsA in a variety of clinical settings.

The first section of the GRAPPA dermatology session centered on the development, validation, and evaluation of screening tools for detecting PsA in the dermatology population. The purpose of this section was to critically examine the available screening tools for PsA and to evaluate their utility among diverse clinical settings.

Abrar Qureshi (Brigham and Women's Hospital, Boston) presented an overview of PsA screening tools. Since the 1990s, PsA screening tools that have been developed include the Psoriatic Arthritis Questionnaire (PAQ; Canada and Sweden)[5], the Psoriatic Arthritis Screening and Evaluation (PASE; USA)[6,7,8], the Psoriatic Arthritis Screening Questionnaire (PASQ; Canada)[9], the Psoriasis Epidemiology Screening Tool (PEST; UK)[10], and the Toronto Psoriatic Arthritis Screening questionnaire (ToPAS; Canada)[11]. Discussion focused on 3 of these screening instruments — PASE, PEST, and ToPAS. All 3 were developed to identify PsA with greater likelihood but were not meant to determine a definite diagnosis or to substitute for a rheumatologic examination.

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The purpose of the PASE questionnaire is to help dermatologists identify patients who may benefit from timely referral to a rheumatologist for evaluation of PsA. Specifically, it was developed to screen known psoriasis patients for inflammatory arthritis. The PASE questionnaire was validated at a combined dermatology-rheumatology clinic at Brigham and Women's Hospital in Boston[6]. The questionnaire comprises 15 multiple-choice questions from 2 subscales that assess symptoms and function separately. Each question is scored on a scale of 1–5, with higher numbers representing greater disease severity. A PASE supplement specifically assesses involvement of axial disease. An initial validation study using a total score cutoff of 47 showed that the PASE questionnaire had 82% sensitivity and 73% specificity to detect PsA in the combined dermatology-rheumatology clinic[6]. When evaluation using the PASE was limited to patients with active symptoms, the PASE questionnaire was able to detect PsA with 93% sensitivity and 80% specificity, with overall area under the receiver operating characteristic (ROC) curve (AUC) of 0.884[8]. Of note, when used in the PRISTINE study[12], the PASE questionnaire showed discrimination and responsiveness to change in disease severity in patients with psoriasis treated with etanercept.

The PEST was developed by Helliwell, *et al*, University of Leeds, UK[10], using questions derived from the PAQ[13]. The initial set of questions and a drawing of a homunculus were sent to patients with psoriasis identified from an electronic database of 2 general practices in Bradford, West Yorkshire, UK. A group of patients with psoriasis was randomly selected from this cohort for in-person examinations by rheumatologists for diagnosis of PsA using the CASPAR criteria. As a result of this study, the initial questions were refined to produce the final PEST instrument, consisting of 5 questions and a homunculus. The PEST was found to be 92% sensitive and 78% specific for detecting PsA, with an AUC of 0.91 (95% CI 0.86–0.97)[10].

The ToPAS was developed to screen for PsA among patients with known psoriasis, as well as the general population[11]. Initial questions were developed based on expert opinions from rheumatologists and dermatologists; the questions were modified for greater clarity and face validity based on additional input from epidemiologists, patients, and other rheumatologists. The ToPAS contains questions on pain and stiffness in the joints and back as well as pictures of psoriasis and psoriatic nail lesions[11]. It was administered to patients attending 5 different clinics: PsA, psoriasis, general dermatology, general rheumatology (excluding patients with PsA), and family medicine. Based on analyses from these clinics, the authors developed a simplified discriminatory score and determined a single cutpoint. The instrument yielded an overall sensitivity of 86.8% and specificity of 93.1%, with AUC of 0.95[11]. The ToPAS is currently being used in a phase 4 study, PSOLAR [PSOriasis Longitudinal Assessment and Registry (http://clinicaltrials.gov/ct2/show/NCT00508547)] that evaluates the safety of ustekinumab and infliximab in patients with moderate to severe psoriasis.

Comparison of Psoriatic Arthritis Screening Instruments

Due to differences in study settings and participant populations where the PASE, PEST, and ToPAS were validated, comparison of instrument performance from these initial validation studies can be problematic. Therefore, head-to-head comparisons of PsA screening instruments in the same patient population are necessary to adequately determine relative performance.

In a study comparing ToPAS and PASE for detection of PsA in patients with psoriasis, 83 members of the Dutch Psoriasis Society completed both instruments; 33 of these participants were diagnosed with PsA by rheumatologists. The AUC for PASE was 0.75 (95% CI 0.65–0.86), whereas the AUC for ToPAS was 0.85 (95% CI 0.76–0.93)[14]. Both instruments performed well and are suitable for screening for PsA.

Philip Helliwell (University of Leeds, UK) presented preliminary data from an ongoing study comparing PsA screening performance among 3 instruments: PASE, PEST, and ToPAS. The CONTEST (Comparison of Three Screening Tools) study, led by a team of investigators from the UK, includes study sites in Leeds, Bath, London, Newcastle, Glasgow, Manchester, and Bradford; the 3 PsA screening instruments (PASE, PEST, and ToPAS) were distributed to the psoriasis clinics at these sites. The questionnaire packs were randomized by instrument order. The inclusion criteria were age ≥ 16 years, the ability to read and understand English, psoriasis diagnosed by a dermatologist, and no previous diagnosis of PsA. Those with an established diagnosis of PsA were excluded.

Dr. Helliwell reported that, at the time of the meeting, 306 of the 581 questionnaire packs that were distributed had been returned. A total of 147 participants were screened positive for PsA by any instrument; 78 were examined in person by rheumatologists, and 17 were confirmed to have PsA. Data from the CONTEST were being analyzed at the time of preparation of this article.

Panel Discussion on Psoriatic Arthritis Screening Instruments

A panel of dermatologists and rheumatologists engaged in a spirited discussion regarding screening for PsA among patients with psoriasis, with active participation from the other GRAPPA members in the audience. The discussion panel, moderated by April Armstrong (University of California, Davis), included Drs. Qureshi and Helliwell, and Amit Garg (Boston University), Dafna Gladman (University of Toronto and Toronto Western Research Institute), and Alice Gottlieb (Tufts Medical Center, Boston).

The first topic was the relative strengths of PASE, PEST, and ToPAS. Panel members considered PASE to be a sensitive instrument with responsiveness to disease activity. Compared to other instruments, the functional assessment component of the PASE was unique. Similarly, the panelists found PEST to be very brief and highly sensitive. The PEST had the least number of questions; its homunculus was considered readily interpretable and easy for patients to annotate. The ToPAS was tested in several settings ranging from specialty clinics to primary care clinics, and was considered sensitive, specific, and easy to complete.

Next, the panelists were asked to comment on how readily these screening tools would be adopted in real-world practices. While dermatologists specializing in psoriasis may use these tools effectively in clinical practice, other dermatologists may have less incentive to adopt a PsA screening tool in their busy clinics. Due to increasing time constraints for dermatology appointments, a utilizable PsA screening tool needs to be valid and brief. Because all 3 PsA screening tools are self-administered by patients, questionnaire completion will not necessarily require extra appointment time if completed prior to their visit. Potential difficulties in adopting a PsA screening tool also may arise from how dermatologists address the additional information elicited by these questionnaires. For example, if a patient responds affirmatively to some symptom questions but does not meet the criteria for referral to a rheumatologist, do these positive responses obligate the dermatologist to initiate further investigation? These considerations continue to highlight the need for a sensitive and specific instrument that will facilitate timely evaluation of the patient for PsA; importantly, its adoption in real-world clinical practice will depend greatly on brevity.

Lastly, panelists considered whether a questionnaire-based PsA screening tool should be combined with basic joint assessments by dermatologists in order to better recognize PsA. Although assessments by dermatologists were thought likely to lead to earlier, more accurate recognition of PsA, panelists had divergent views on whether dermatologists without a special interest in psoriasis would be interested in performing joint assessments. Most GRAPPA members agreed that educating dermatologists on joint assessment would be a worthwhile effort. Although the initial group performing joint examinations may be limited to those specializing in psoriasis, with increasing education on PsA, more dermatologists will be able to perform joint assessments, resulting in timely recognition of PsA and improved patient outcomes over time.

Psoriasis Comorbidities

Through a preconference poll, the GRAPPA dermatology members expressed considerable interest in advancing research in psoriasis comorbidities. This field of research has evolved rapidly over the past 10 years, with increasing epidemiologic and translational findings that have advanced our understanding of cardiovascular (CV), autoimmune, and psychiatric comorbidities. Joel M. Gelfand (University of Pennsylvania) began this section with an update on this topic.

Epidemiologic studies have shown that severe psoriasis is associated with an approximately 50% increase in mortality risk and 5 years of life lost[15]. The top causes of death among patients with psoriasis include CV disease (34%), infection (22%), and cancer (21%)[16]. Specifically, compared to the general population, severe psoriasis confers an additional 6.2% absolute risk of 10-year rate of major CV events[17]. This additional risk of adverse CV outcomes attributable to severe psoriasis is similar to that from diabetes[17,18].

The paradigm for the association between psoriasis and CV diseases is continually being updated and elucidated[19,20]. Environmental factors, such as smoking, may contribute to both the risk of developing psoriasis and development of CV diseases. Loci and genes that are associated with psoriasis, diabetes, and CV diseases include PSORS 2,3,4, CDKAL1, ApoE4, and TNFAIP3.

Common factors that appear to be shared between psoriasis and CV diseases include Th1 and Th17 pathways. The increased uric acid and oxidative stress in epidermal proliferation found in psoriasis may also contribute to exacerbation of CV diseases. Endothelial dysfunction appears to be present in both psoriasis and coronary artery disease. Novel applications of Fluorine-18– FDG-PET/CT (2-fluoro-2-deoxy-d-glucose positron emission tomography and computed tomography) have shown that, compared to those without psoriasis, psoriasis patients demonstrate vascular inflammation equivalent to 2 additional decades of aging[21]. Further, FDG-PET/CT revealed subclinical inflammation in the liver and joints in patients with psoriasis with normal liver function enzymes and C-reactive protein. Finally, systemic medications used for psoriasis may positively or negatively affect outcomes for CV diseases.

The majority of new literature supports the association between psoriasis and CV disease independent of CV risk factors[18,22,23]. Additionally, studies continue to define the relationship of psoriasis with metabolic disease. One recent study in a rheumatology clinic in China found that the adjusted odds ratio for the metabolic syndrome in PsA was 2.44 (95% CI 1.48–4.01, $p < 0.001$) relative to patients with rheumatoid arthritis (RA) or ankylosing spondylitis[24]. Additional studies have found that the increasing body surface area (BSA) involvement with psoriasis is correlated with increasing adjusted odds of metabolic syndrome[5]. Specifically, serum triglycerides, blood glucose, and obesity increased in a dose-dependent manner based on psoriasis severity independent of traditional risk factors. New cohort studies continue to support an increased risk of diabetes among patients with psoriasis compared to those without psoriasis[25].

There is increasing focus on investigating metabolic disorders associated with pediatric psoriasis. In a population study using a large health maintenance organization database to examine whether obesity and CV risk factors were associated with psoriasis in children and adolescents[26], investigators found that overweight and obesity were associated with higher odds of psoriasis in youth and that adolescent patients with psoriasis had higher serum lipids (cholesterol, low density lipid protein, and triglycerides) independent of body weight[26].

Finally, we examined the literature on whether treatment of psoriasis improves metabolic and CV disease outcomes. Much of our understanding of how systemic therapy used for autoimmune diseases affects patients' CV risks and outcomes comes from the RA literature. A systematic review suggests that methotrexate use in patients with RA is associated with a reduction in CV events[27]. Recent reviews, however, have suggested that the effect of tumor necrosis factor (TNF) inhibitors on reducing CV risk in patients with RA is inconclusive and requires further study[28].

The literature examining how systemic therapy in psoriasis affects CV outcomes is limited. One large retrospective cohort study found that, compared with psoriasis or RA patients prescribed nonbiologic disease-modifying antirheumatic drugs (DMARD), the risk for developing diabetes was lowest among those on TNF antagonists[29]. Specifically, the adjusted hazard ratios for diabetes were 0.62 (95% CI 0.42–0.91) for TNF inhibitors, 0.77 (95% CI 0.53–1.13) for methotrexate, and 0.54 (95% CI 0.36–0.80) for hydroxychloroquine compared with other nonbiologic DMARD.

Panel Discussion on Psoriasis Comorbidities

Dr. Armstrong moderated a panel discussion of psoriasis comorbidities; panelists included Drs. Garg, Gelfand, Gottlieb, and Kristina Callis Duffin (University of Utah). First, panelists discussed how dermatologists screen patients with psoriasis for comorbidities in their practices. Some panelists reported that they counseled patients routinely regarding the increased risk of CV diseases during dermatology visits and advised patients to have regular primary care visits to screen for and monitor CV comorbidities. Some reported that they measured patients' blood pressure at least once a year and counseled them on obesity and smoking cessation. Others collected information on comorbidities systematically, using an intake form with inquiries about CV risks and events as well as non-CV comorbidities. The panelists expressed concerns that, while dermatologists specializing in psoriasis may routinely inquire about comorbidities, this practice might not necessarily reflect routines of most dermatologists. Although most dermatologists are not expected to actively manage comorbidities, educational efforts are necessary to enable dermatologists to make timely referrals for evaluation of these conditions.

Next, the panelists discussed whether a randomized controlled trial (RCT) was necessary to determine whether successful control of psoriasis would lower the risk of CV events and/or mortality. While findings from the CORRONA study and the Kaiser Permanente study suggest that TNF antagonists are associated with a decreased risk of CV diseases[30,31], an audience poll showed that about half of GRAPPA members were convinced by this evidence while the other half were skeptical. The panelists agreed that an RCT examining how psoriasis treatments affect CV diseases and mortality would yield highly valuable information. However, such a trial would likely require following thousands of patients over a 3–5 year period and therefore be highly resource-intensive. One less expensive option would be to examine surrogate markers for clinical outcomes of comorbid conditions. If the funding were available, an RCT of intensive control versus usual care of psoriasis was suggested to determine if intensive control of psoriasis would lead to improved outcomes in comorbidities.

Frontiers in Genetics and Comparative Effectiveness Research

Frontiers in psoriasis genetics. Epidemiologic studies have shown that the age of onset of psoriasis has 2 peaks, with the larger peak between 20 and 30 years of age and a smaller peak between 50 and 60 years. This observation and analysis of data has led to the belief that patients with earlier onset of disease (type I) may have a stronger family history and more severe disease, whereas those with later-onset psoriasis (type II) often have a sporadic form with milder disease[32]. From these epidemiologic observations, the study of genetics of psoriasis has progressed over the past few decades with novel techniques to elucidate the genetic basis for psoriasis. Genetic linkage studies, which utilized families with multiple affected members, initially identified 10 regions of shared susceptibility (PSORS1 to 10).

Genome-wide association studies (GWAS) have identified more than 25 genetic variants that associate with psoriasis[33]. Pathways that have been implicated from GWAS include interleukin 23 (IL-23) signaling (*IL12B*, *IL23R*), nuclear factor-κB (NF-κB) signaling (TRAF3IP2), and antigen presentation by the major histocompatibility complex (MHC)[34,35]. However, because most of these variants are common (often seen in patients without psoriasis) and are often not in coding regions, GWAS is limited in finding rare variants or determining causal variants.

Few loci have been consistently identified across the different linkage studies, thereby giving credence to probability of their representing true psoriasis loci. For example, the only locus that has been consistently identified in all GWAS is MHC Class I, which maps to human chromosome 6p21 (*PSORS1*). Among the identified loci, *PSORS1* has the highest OR (OR ~3) associated with the development of psoriasis and PsA and accounts for 30%–50% of the genetic contribution to psoriasis[36]. Despite the recent discoveries from

GWAS, the combined genetic risk from GWAS for psoriasis accounts for only about one-third of the genetic basis of psoriasis. Therefore, one key question is how rare genetic variants may account for part of the missing heritability.

Anne Bowcock (Washington University, St. Louis) presented her work on identification of novel genes mutated in psoriasis and PsA, focusing on the discovery of *PSORS2*. In 1994, Bowcock's group performed a genome-wide linkage scan on 3 generations of a large family in which 20 members were diagnosed with psoriasis and PsA. A novel locus responsible for psoriasis was identified in this family, mapping to the end of human chromosome 17q25[37]. Using genomic capture and sequencing techniques, the Bowcock group has now determined that a mutation in the *PSORS2* region accounts for the cases of psoriasis and PsA seen in this family. A second psoriasis family from Taiwan and a sporadic case of a child with severe pustular psoriasis were also found to have a *de novo* mutation in the same gene.

Further functional studies of this gene have revealed that it encodes a gene product that activates the NF-κB pathway. The rare gain of function mutations in this gene lead to enhanced NF-κB signaling. Common polymorphisms within the gene are also associated with psoriasis and PsA susceptibility. It is possible that functional variants in this gene lead to psoriasis and PsA through a failure to maintain homeostasis in response to an inflammatory stimulus in the skin and joints.

Novel Methods in Comparative Effectiveness Research

The Institute of Medicine defines comparative effectiveness research (CER) as the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor health conditions[38]. More simply put, CER seeks to identify what works for which patients under what circumstances. With the discovery of novel therapies for psoriasis, increasing need emerges for CER among the various treatments to inform clinicians and patients. While traditional psoriasis RCT have compared new therapies to placebo, in real-world settings, comparisons to existing treatments or other novel treatments are likely more clinically relevant.

Methods for CER vary widely and include observational studies, RCT, and metaanalyses. In psoriasis, because head-to-head RCT between different treatments are usually not available, alternative forms of analysis are necessary to understand how treatments may compare with one another. Indirect comparisons provide opportunities for comparative effectiveness analyses in the absence of head-to-head trials.

Aside from conventional metaanalyses, indirect comparisons can be categorized into 2 forms based on the availability of patient-level data. In the first form, the investigators have access to patient-level data for Drug A and only aggregate data for Drug B. In the second form, the investigators have access to patient-level data for both Drug A and Drug B from 2 separate clinical trials. In the current environment, the first form of indirect comparison is more feasible because pharmaceutical companies do not routinely disclose patient-level data to one another.

GRAPPA members reviewed the first form of indirect comparison, where patient-level data are available for Drug A and only aggregate data are available for Drug B. Because biases can arise from imbalances among different trials, novel methods that account for these imbalances will likely expand applicability of indirect comparisons and provide clinically relevant analyses. To illustrate this form of indirect comparison in psoriasis, an article by Signorovitch, *et al*[38] was reviewed.

The authors performed an indirect comparison using patient-level data from the adalimumab trials (REVEAL and M02-528)[39,40] and aggregate data from the etanercept trial[41] for treatment of moderate to severe psoriasis. The matching method in indirect comparison requires development of a logical approach to sample selection — the first step in the analytic process. In general, trials with patient-level data should have inclusion and exclusion criteria that are as inclusive as, or more inclusive than, trials with only aggregate data. For example, if the trial with patient-level data included patients < 55 years old, indirect comparison to trials with aggregate data that recruited patients age < 50 years would be feasible. However, comparison to other trials that recruited patients > 55 years old would be difficult due to the inability to adequately balance age distributions between trials. In the analysis by Signorovitch, patients from the adalimumab trials were pooled and subjected to the same inclusion and exclusion criteria as those reported in the etanercept trial[41].

If the selection of baseline characteristics is similar between the 2 trials, mean baseline characteristics between the trials can be matched. All baseline characteristics between the etanercept and adalimumab patient populations were selected for matching, with the exception of global assessment scores, where the trials used different scales. As expected, the baseline characteristics of the etanercept-treated and adalimumab-treated patients revealed some differences. For example, compared to the etanercept-treated patients, adalimumab-treated patients were younger, and had less prior systemic or phototherapy, lower mean affected BSA, and higher prevalence of PsA.

To adjust for the differences in baseline characteristics, Signorovitch proposed a method to re-weight patients individually from the trials with available patient-level data to match those from trials with only aggregate data. Methodologists first focused on the treatment arms from the trials, and planned to incorporate information from placebo arms at a later stage. Each patient from the treatment arm had 3 vectors that characterized the patient: (1) X = baseline characteristics of the patient, (2) T = treatment received (either adalimumab or etanercept), and (3) Y = outcome of interest.

Since patient-level data were available only for adalimumab-treated patients, only patients in that group were re-weighted to match the distribution of patients receiving etanercept. The weight assigned to individual patients in the adalimumab-treated group represented the odds that a patient would enroll in the etanercept trial over the adalimumab trial given his or her baseline characteristics. The consequence of the re-weighting was that patients who were more likely to receive etanercept were up-weighted to compensate for their underrepresentation in the adalimumab group, whereas those less likely to receive etanercept were down-weighted to compensate for their overrepresentation in the adalimumab group. Thus, each patient was re-weighted by the estimated odds of receiving etanercept versus adalimumab. Placebo-arm data were also matched on baseline characteristics across the trials and were incorporated by applying adjusted indirect comparison.

This matching procedure resulted in the exact match of the means and standard deviations for all available baseline characteristics between the trial populations. The same weighting procedure was also applied to the outcomes of the trial. For example, the matching procedure resulted in about 0.5% reduction in PASI 75 response (Psoriasis Area and Severity Index 75% improvement) to adalimumab and about 1% reduction in PASI 75 response of the corresponding placebo arm of the adalimumab trial, which led to similar placebo response rates between the trials. The match-adjusted indirect comparison showed that adalimumab was associated with a 17.2% higher PASI 75 response rate compared to etanercept[38].

The advantages of match-adjusted indirect comparisons include exact balance of the mean and standard deviations of baseline characteristics across the trials, thereby eliminating first-order confounding due to the observed patient characteristics and second-order confounding due to linear combination of observed characteristics. The limitations of match-adjusted indirect comparison include potential residual confounding due to unobserved differences between trials that affect treatment-arm but not placebo-arm outcomes. Before this method of indirect comparison can be put to widespread use, it will have to be further critiqued to determine its advantages and limitations; any observed differences in effectiveness arising from this type of analysis need to be assessed for clinical relevance and consequence.

Conclusion

GRAPPA members led engaging and productive discussions on priority research areas in psoriasis and PsA, focusing on evaluation of PsA screening tools, psoriasis comorbidities, genetics, and comparative effectiveness research. Continued investigative efforts in these important areas will likely lead to advanced understanding of the disease process, development of safer and more effective therapeutic options, and improved clinical outcomes.

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