DRUGS IN RESEARCH

Pharmacologic and Bacteriologic Properties of SCH-27899 (Ziracin), an Investigational Antibiotic from the Everninomicin Family

David R. Foster, Pharm.D., and Michael J. Rybak, Pharm.D., FCCP

SCH-27899 is an investigational antibiotic from the everninomicin family, a group of oligosaccharide antibiotics produced by *Micromonospora carbonacea*. Information regarding the pharmacology, pharmacodynamics, pharmacokinetics, efficacy, and toxicity of this agent was obtained from a MEDLINE search and a review of abstracts presented at recent scientific meetings. SCH-27899 has in vitro bacteriostatic activity against a wide variety of gram-positive organisms, including highly resistant organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate-sensitivity *S. aureus*, *Streptococcus pneumoniae* (both penicillin-susceptible and -nonsusceptible), and vancomycin-resistant enterococci. In vitro data, animal studies, and preliminary human studies indicate that it is effective and fairly well tolerated. Its place in therapy remains to be determined, and clinical trials continue.
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SCH-27899 (Ziracin; Schering-Plough Research Institute, Kenilworth, NJ) is an investigational

From the Department of Pharmacy Practice, College of Pharmacy and Allied Health Professions (both authors); and the Department of Internal Medicine, Division of Infectious Diseases, School of Medicine (Dr. Rybak), Wayne State University; and The Anti-Infective Research Laboratory, Department of Pharmacy Services, Detroit Receiving Hospital/University Health Center (Dr. Rybak); Detroit, Michigan; and the College of Pharmacy, University of Michigan, Ann Arbor, Michigan (Dr. Foster).

Address reprint requests to Michael J. Rybak, Pharm.D., The Anti-Infective Research Laboratory, Department of Pharmacy Services (1B), Detroit Receiving Hospital/University Health Center, 4201 Antoine Boulevard, Detroit, MI 48201; e-mail: mrybak@dmc.org.

antibiotic from the everninomicin family. The everninomicins are oligosaccharide antibiotics produced by *Micromonospora carbonacea*, which consists of at least five distinct compounds (everninomicins A, B, C, D, E) that have activity against gram-positive organisms.[1] Everninomicin D is the most active of these compounds and is highly active against gram-positive bacteria; it is the D component to which SCH-27899 is most closely related.[1–3] The antimicrobial potential of the compounds was first recognized over 30 years ago, but emergence of widespread microbial resistance to commonly prescribed antimicrobial agents has sparked a new interest.

Chemical Characteristics and Pharmacology

Everninomicins have several unusual structural features, such as the presence of ortho ester functionalities, an aliphatic methylene dioxy group, a nitro sugar, and a fully substituted phenolic ester residue.[4] The structure of SCH-27899 ($C_{70}H_{97}NO_{38}Cl_2$) is shown in Figure 1. It is an amorphous solid with an estimated

molecular weight of 1629 d.[3]

The mechanism of antibacterial action of the everninomicins is not well described, although it is believed that the agents act to inhibit protein synthesis. In a recent investigation of *Staphylococcus aureus* isolates exposed to SCH-27899, in vivo incorporation of isoleucine was markedly reduced. As incorporation of other substrates (thymidine, uracil, *N*-acetylglucosamine, acetate) was not affected to the same extent as isoleucine, the authors concluded that this is consistent with the hypothesis that the drug inhibits protein synthesis.[5] By identifying a point mutation common to strains of *Streptococcus pneumoniae* resistant to SCH-27899, it was theorized that the drug's target site is ribosomal protein L16, located at the interface of the large and small ribosomal subunits.[6] The proposed mechanism of action involves a ribosomal target; thus it is likely that the agent's actions are concentration independent.

Spectrum of Antibacterial Activity and Pharmacodynamics

Since the compounds were first isolated, it was recognized that everninomicin D is highly active against many gram-positive organisms, with little or no gram-negative activity, an observation that was confirmed in later studies.[1, 2] More recent studies with SCH-27899 showed in vitro antibacterial activity against a wide variety of gram-positive organisms, with bacteriostatic actions on methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate-susceptibility *S. aureus* (VISA), methicillin-sensitive *Staphylococcus epidermidis* (MSSE), methicillin-resistant *S.*

epidermidis (MRSE), penicillin-susceptible and -nonsusceptible strains of *S. pneumoniae, Streptococcus pyogenes*, vancomycin-sensitive enterococci, vancomycin-resistant enterococci (VRE), *Listeria monocytogenes, Clostridium jeikium,* and *Clostridium difficile.*[7–9]

The antimicrobial activity of the agent compared with that of vancomycin is shown in Table 1. In comparative studies, the activity of SCH-27899 was consistently better than that of vancomycin for the organisms listed.[7, 8] In vitro activity of SCH-27899 was compared against a variety of enterococci species (including VRE) with that of several agents, most notably, the investigational RP-59500 (quinupristin-dalfopristin, Synercid; Rhône-Poulenc Rorer, Collegeville, PA), vancomycin, and teicoplanin.[10] The minimum inhibitory concentrations for 90% of tested strains (MIC_{90}) for SCH-27899 (0.25–0.5 µg/ml) were at least 4-fold lower than those of RP-59500 (2.0–16 µg/ml) in all species tested. Values for vancomycin were 4.0–512 µg/ml and those for teicoplanin were 0.5–128 µg/ml or below. When SCH-27899 was compared with levofloxacin, trovafloxacin, ciprofloxacin, and sparfloxacin, it had superior in vitro activity (higher therapeutic index, based on comparison with ratios of drug concentration and MIC) against penicillin-intermediately susceptible and penicillin-nonsusceptible strains of *S. pneumoniae.*[11]

In addition, SCH-27899 appears to have substantial in vitro activity against *Legionella* sp.[12, 13] In a study of 104 *Legionella* sp, its MIC_{90} was 0.25 µg/ml, comparable with those of ofloxacin (0.06 µg/ml) and erythromycin (0.05 µg/ml). In an in vitro investigation involving
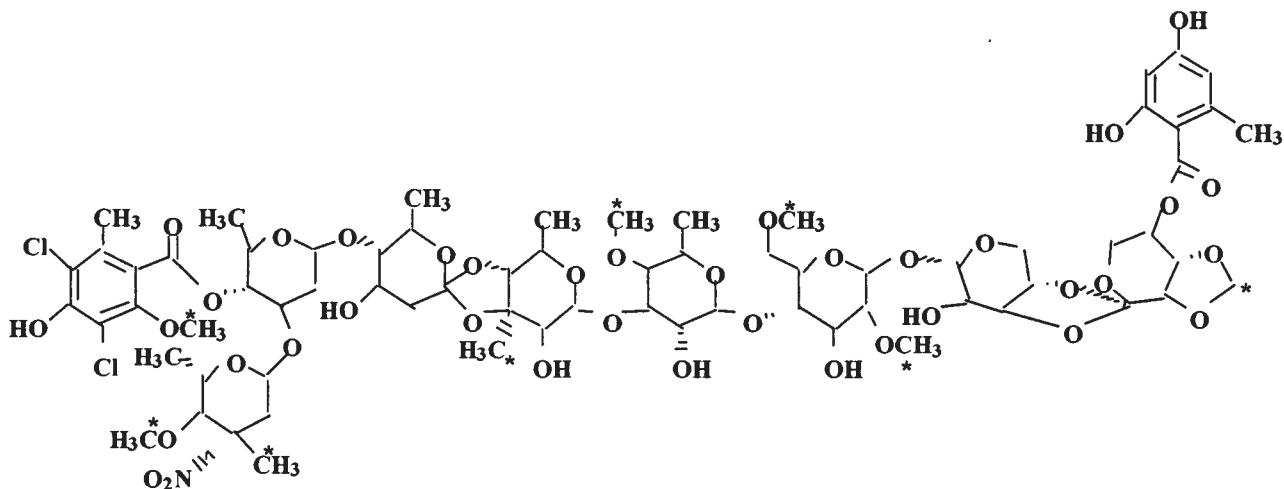

Figure 1. Structural formula of SCH-27899.

Table 1. Comparative In Vitro Susceptibilities of SCH-27899 and Vancomycin

Organism	MIC$_{90}$[a] (range, µg/ml)	
	SCH-27899	Vancomycin
S. aureus		
Methicillin susceptible	0.44 (0.05–0.5)	0.75 (0.2–2)
Methicillin resistant	0.66 (0.05–0.5)	0.75 (0.2–4)
VISA[b]	0.5	4.0
Coagulase-negative staphylococci[c]		
Methicillin susceptible	0.66 (0.25–0.78)	2.37 (0.1–4)
Methicillin resistant	0.66 (0.1–3.13)	2.65 (0.1–3.13)
Enterococci		
Vancomycin susceptible[d]	0.25 (< 0.125–0.5)	2.0 (0.5–2.0)
E. faecalis[7]	0.2 (0.05–0.39)	1.56 (0.2–3.13)
E. faecium[7]	0.39 (0.05–0.39)	1.56 (0.01–1.56)
E. avium[7]	0.2 (0.05–0.39)	0.39 (0.1–0.78)
Vancomycin resistant[e]	0.25 (< 0.125–0.5)	> 8.0 (8.0 to > 8.0)
Streptococcus pyogenes	0.113 (< 0.025 to < 0.125)	0.32 (0.1–0.5)
Streptococcus pneumoniae	0.111 (< 0.025 to < 0.125)	0.50 (0.1–0.78)
Streptococcus agalactiae	0.111 (< 0.025 to < 0.2)	0.554 (< 0.125–0.78)
Streptococcus group C[8]	< 0.125 (< 0.125)	0.25 (0.25–0.5)
Streptococcus group G[8]	< 0.125 (< 0.125)	0.125 (< 0.125–0.125)
Clostridium jeikium[8]	< 0.125 (< 0.125)	< 0.125 (< 0.125)
Clostridium difficile[7]	0.2 (0.05–0.2)	1.56 (0.1–1.56)
Listeria monocytogenes[8]	< 0.125 (< 0.125–0.25)	0.5 (0.25–0.5)

[a]MIC$_{90}$ = minimum inhibitory concentration for 90% of strains tested[7–9]; where possible, it represents a weighted average of information from references 7 and 8.

[b]Vancomycin-intermediate-susceptibility *S. aureus* (no ranges reported).[9]

[c]Isolates tested were *S. epidermidis*, *S. saprophyticus*, *S. hominis*, and *S. capitis*,[5] and *S. epidermidis* only.[7]

[d]*E. faecium* and *E. faecalis*.[8]

[e]*E. faecium* only.[8]

anaerobic organisms, SCH-27899 had significant antibacterial activity against *Peptostreptococcus* sp (MIC$_{50}$ < 0.25 µg/ml) and was active against *Porphyromonas* sp (MIC$_{50}$ 2 µg/ml; it was less active than piperacillin, clarithromycin, clindamycin, and metronidazole). However, SCH-27899 had poor activity against *Bacteroides fragilis* and *Fusobacterium nucleatum*.[14] It had in vitro activity against *Borrelia burgdorferi*, comparable with those of penicillin and ceftriaxone (MIC$_{90}$ 0.1–0.5, 0.5–2, and 0.1–0.25 µg/ml, respectively).[15]

The agent does not appear to have appreciable in vitro activity against atypical organisms; its MIC$_{90}$ against *Mycoplasma pneumoniae* was 16 µg/ml, and the compound was less active than macrolides and fluoroquinolones.[16] Similarly, MIC$_{90}$ values for SCH-27899 were 8.0 µg/ml against *Chlamydia pneumoniae* and *Chlamydia trachomatis*.[17] SCH-27899 was less active than doxycycline and erythromycin against both *Chlamydia* sp.

Attempts were made to quantify the post-antibiotic effect (PAE) of SCH-27899. The drug was removed through a 1/100 dilution in antibiotic-free Mueller Hinton broth after 1-hour exposure to bacterial isolates.[7] The PAE was quantified by performing viable cell counts every hour for 8 hours and comparing the difference in time required by test and control cultures to increase 1 log$_{10}$ colony-forming unit (CFU)/ml after the drug was removed. At a concentration of 4 times its MIC, the PAE of SCH-27899 was 1.8 hours against *S. aureus* and 2.6 hours against *E. faecalis*. These values were slightly longer than those of vancomycin for the same organisms (1.5 and 2.2 hrs, respectively). It is unlikely, however, that this difference in PAE is of clinical significance.

Studies examined the in vitro activity of SCH-27899 in combination with other drugs. Seventeen antimicrobial agents were screened for either synergy or antagonism with SCH-27899 in a collection of 110 bacterial isolates representing 31 species or subgroups.[18] No evidence of either antagonism or synergy was observed, with one potential exception; the addition of SCH-27899 to ampicillin produced at least a 4-fold decrease in ampicillin MICs in four of six methicillin-susceptible staphylococci isolates. Unfortunately, this study is published only in abstract form and does not report the investigators' detailed methods. Others have examined combined antimicrobial activity of SCH-27899 with various

β-lactam antibiotics and fosfomycin (an antibiotic produced by *Streptomyces* strains) against strains of MRSA and MRSE using the microdilution checkerboard method.[7] Synergy (30–56% of strains), additive effects (11–37%), or indifference (19–37%) was observed with all combinations, with no evidence of antagonism.

A study was conducted that examined the effect of changes in the growth medium on the in vitro actions of SCH-27899. It demonstrated that minor changes in inoculum (a decrease of 10^3 CFU/spot or an increase of 10^5 CFU/spot), an increased magnesium concentration, and an alkaline pH (pH = 8) resulted in less than a 2-fold change in the agent's MIC values.[19] These values showed no change or up to a 4-fold decrease when the agent was placed in an acidic environment (pH = 6), incubated in an anaerobic environment, and incubated in the presence of 5% carbon dioxide. Increasing the inoculum to greater than 10^6 CFU/spot and the addition of 5% sheep blood to the agar markedly diminished the activity of SCH-27899.

In a study conducted to derive preliminary interpretive criteria for susceptibility testing of SCH-27899 using the disk diffusion technique, disk zone diameters of inhibition were correlated with MICs of selected gram-positive and gram-negative organisms.[20] The greatest correlation was seen with a test disk concentration of 5 μg. For a break point of less than 2 μg/ml of SCH-27899, susceptibility was defined as a zone larger than 12 mm, intermediate susceptibility as a zone of 10–11 mm, and resistance as a zone less than 9 mm. Initially, due to limited solubility of SCH-27899 in growth media, the manufacturer recommended the E-test method to determine susceptibilities.[21] Subsequent investigations, however, recorded excellent correlation for susceptibility testing by broth microdilution and agar dilution methods.[21] The manufacturer of SCH-27899 proposed susceptibility criteria, with 2 or less representing susceptibility, 4 representing intermediate susceptibility, and 8 or greater indicating resistance.[21]

Resistance

The long-term utility of any antimicrobial agent depends not only on its antimicrobial activity and safety profile but also on the ease with which resistance to the drug develops. Although naturally occurring resistance to SCH-27899 among organisms normally considered susceptible to the agent has not been observed,

preliminary studies with this compound and the everninomicins indicated the potential for organisms to develop laboratory-induced resistance. Resistance occurred when *S. aureus* strains that were initially susceptible to everninomicin D were serially transfused into increasing concentrations (2-fold dilutions) of everninomicin D in liquid medium.[2] The authors recovered organisms that grew in 32 μg of everninomicin D/ml. Similarly, when strains of MSSA, MRSA, and *E. faecalis* were exposed to subinhibitory concentrations (1/16 MIC) of SCH-27899, resistance developed, but in all cases it did not exceed more than 4 times the original MIC for the organism.[7] In both studies, resistance appeared in a slow, stepwise fashion.

Pharmacokinetics

The pharmacokinetics of SCH-27899 in humans are best described by a three-compartment model. The compound is eliminated primarily through hepatic transformation to microbiologically inactive glucuronide and sulfate conjugates, approximately 6% is eliminated unchanged in urine, and 4% is eliminated unchanged in feces. Due to assay limitations, the terminal elimination phase half-life cannot be calculated reliably, but it was reported to be approximately 10 hours. The agent has a high degree of protein binding (96%) to albumin in vitro and appreciable tissue distribution in vivo, although the exact percentage bound to protein in vivo is unknown.[21] In a pharmacokinetic study in humans, SCH-27899 was administered to individuals with various degrees of renal function. Twenty subjects with creatinine clearance ranging from below 15 ml/min/1.73 m^2 (dialysis) to greater than 80 ml/min/1.73 m^2 were placed into five groups based on renal function (4 patients/group). Half-life was similar in all groups, ranging from 8.34–9.83 hours, and the compound was not dialyzable.[22] These results suggest that no dosage adjustment is required in patients with renal insufficiency. Early studies of the closely related compound everninomicin D found poor oral availability and erratic intramuscular absorption. As a result, the intravenous route likely will be the only feasible method of administration.[23]

Efficacy

Most available data concerning SCH-27899 come from in vitro and animal studies. Studies

using in vitro pharmacodynamic models attempted to derive appropriate dosing regimens. These models were designed to expose cultures to a gradient of antibiotic concentrations to simulate the drug's serum pharmacokinetics. In one such model, various dosing regimens were tested on isolates of MRSA, MRSE, *S. haemolyticus*, penicillin-nonsusceptible *S. pneumoniae*, ampicillin-resistant *E. faecalis*, Van-C-producing *Enterococcus gallinarum*, and Van-A-producing *E. faecium*.[24] Concentrations of SCH-27899 were used to simulate single dosages of 3, 6, and 10 mg/kg/day, and multiple-dose regimens of 3 and 6 mg/kg twice/day. All dosages were effective in achieving a kill of 4 log or better with MRSA or MRSE strains with MIC of 1 µg/ml, whereas only 10 mg/kg/day and 6 mg/kg twice/day achieved the same effects in *S. haemolyticus* strains with MIC of 2 µg/ml. In *S. haemolyticus* strains, other regimens produced only 3 log killing. In penicillin-nonsusceptible *S. pneumoniae*, a 3 log kill was achieved with 10 mg/kg/day and 6 mg/kg twice/day. Two-log killing was achieved with 6 and 10 mg/kg/day and 3 and 6 mg/kg twice/day. Simulated dosages of 10 mg/kg/day and 6 and 3 mg/kg twice/day caused a 3 log kill in ampicillin-resistant *E. faecalis* and Van-C-producing *E. gallinarum*. In the case of Van-A-producing *E. faecium*, no killing was observed with any regimen except 10 mg/kg/day, which produced a kill of 1 log. The authors concluded that significant killing could be achieved for all organisms tested with the exception of Van-A-producing *E. faecium*. Although such in vitro models do not always predict in vivo efficacy, they often are useful in deriving initial regimens for preliminary human studies.

In an attempt to evaluate the drug's potential role in the treatment of catheter- and other device-related infections, a strain of MRSA was incubated with different sub-MIC concentrations of everninomicin in combination with fosfomycin.[7] Although the agents had no inhibitory effect at concentrations tested, when the authors compared viable sessile cells on the glass surface with or without the agents after 7 days incubation at 37°C, the number of adherent cells was much smaller in test cultures than in control cultures. Unfortunately, the clinical implications of these findings are unknown; the results were not compared with other antimicrobials, and it is not known whether these in vitro effects are important in vivo.

The in vivo activity of SCH-27899 was studied in several animal models. In a murine model, the agent was markedly effective in treating experimental pneumonia caused by *S. pneumoniae*, and in immunocompromised mice it prevented fatal replication of *Legionella pneumophila* lung infections.[25, 26] In another murine model, its in vivo effects were similar to those of vancomycin and superior to those of placebo in a model of hematogenous pulmonary infection induced by MRSA enmeshed in agar beads.[27]

SCH-27899 was compared with ceftriaxone in a phase II clinical trial involving 55 patients with *S. pneumoniae* pneumonia.[28] Patients were randomized to receive 3 days of SCH-27899 (3 or 6 mg/kg/day intravenously) or ceftriaxone (2 g/day intravenously), followed by a 7-day course of oral amoxicillin. After 4 days, the clinical response rate was 94% for the 3-mg/kg/day SCH-27899 group and 100% for both the 6-mg/kg/day SCH-27899 group and the ceftriaxone group. Bacteriologic response rates were identical to clinical response rates. At the end of antibiotic therapy (days 13–15), 100% of patients receiving both SCH-27899 regimens had clinical cure or improvement, compared with 94% of the ceftriaxone group. All groups achieved eradication or presumed eradication at the end of therapy. All treatments were well tolerated; adverse effects were reported in 4/17 patients treated with SCH-27899 3 mg/kg/day, 7/18 treated with SCH-27899 6 mg/kg/day, and 7/20 treated with ceftriaxone. Unfortunately, this study was published as an abstract and did not describe the adverse effects.

Toxicity

There are few published data regarding the toxicity of SCH-27899. In animal studies, targets of toxicity were kidneys, liver, central nervous system, adrenal glands, lymph nodes, lungs, small intestine, and site of injection.[21] In a single-dose study in humans, the most common adverse effects were dizziness, paresthesias, headache, fatigue, weakness, and gastrointestinal symptoms. No dose-related adverse effects or laboratory changes occurred.[21] When several doses were given to humans, toxicities were injection site reactions, headache, loose stools, fatigue, rhinitis, and gastrointestinal symptoms. Increases in serum creatinine and decreases in creatinine clearance were noted in 3/63 subjects. These tended to occur after approximately 6 days of therapy and returned to baseline after approximately 10 days. Increases in total bilirubin were rarely reported, but they were

considered mild to low and without clinical significance.[21]

Potential Place in Therapy

Widespread administration of antimicrobial agents has led to the development of resistance to the action of many available antibiotics. Gram-positive infections, especially nosocomial infections, are increasingly problematic. Enterococci are intrinsically resistant to many drugs, including fluoroquinolones, cephalosporins, clindamycin, and aminoglycosides.[29, 30] These organisms, in particular *E. faecium* and *E. faecalis,* are associated with urinary tract infections, wound infections, and bacteremias in significant numbers of hospitalized patients. Most alarming, with the emergence of VRE, clinicians are faced with the potential for infections that are resistant to virtually all available agents. Indeed, VRE are a global problem and has diffuse geographic distribution in the United States.[30] In a multicenter study using 1992 data, 23% of centers surveyed reported VRE, and in a 1994 audit of centers not reporting VRE in 1992, 61% reported subsequent emergence of VRE.[31] The optimal treatment of VRE is not well defined. Tetracycline, doxycycline, newer fluoroquinolones, and chloramphenicol have been tried, but both failure and toxicities were reported with these agents.[29, 30]

The investigational RP-59500 is a combination of two antibiotics of the streptogramin family that have activity against both vancomycin-susceptible and vancomycin-resistant strains of *E. faecium*, with less profound effects on *E. faecalis.*[29, 30, 32] The manufacturer of RP-59500 is seeking approval from the Food and Drug Administration.

Resistance among other strains of gram-positive organisms is also widespread. Staphylococci are commonly resistant to penicillins and aminopenicillins, and resistance of *S. aureus* and *S. epidermidis* to penicillinase-resistant penicillins (oxacillin, methicillin) increased drastically in the past several years.[30] In addition, MRSA and MRSE can develop rapid resistance to fluoroquinolones.[30] Vancomycin remains the drug of choice in the treatment of MRSA and MRSE. Although true vancomycin resistance has not yet been reported in a clinical isolate of *S. aureus*, the vancomycin resistance gene was expressed in a strain of the organism, and strains of VISA were reported in the United States.[30, 33]

The frequency of penicillin-nonsusceptible pneumococci increased dramatically in the past several years.[34] Pneumococcal resistance to macrolides may occur, and resistance to the older fluoroquinolones is possible.

SCH-27899 may prove to be useful in the treatment of infections caused by VRE and other highly resistant gram-positive organisms. In vitro susceptibility studies showed that it had activity against VRE, MRSA, MRSE, VISA, and penicillin-nonsusceptible pneumococci.[8, 9, 24] Based on favorable results of animal studies and phase II clinical trials, a double-blind, multicenter, phase III trial of SCH-27899 in *S. pneumoniae* pneumonia is in progress. Also in progress are additional phase II studies, one of which is designed to evaluate the efficacy of the agent in VRE bacteremia and another to test it in gram-positive complicated skin, skin structure, and intravenous catheter infections. The ability to induce laboratory resistance to both everninomicin D and SCH-27899 warrants further study, as does the role of combination therapy and various dosages in the development of resistance. If and when the compound is available for compassionate use, it may play a significant role in the treatment of infections resistant to vancomycin. Although it is not possible at this time to predict its future role, the addition of new agents with activity against organisms highly resistant to conventional drugs is important.

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