Review Article

Antivitamins: A Silver Lining in the Era of Antimicrobial Resistance

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Abstract

Antivitamins are compounds that negate the biological effects of vitamins. They have been successfully exploited for the development of various classes of drugs. In the early 19th century, the antifolate prontosil was developed for the treatment of puerperal fever. Since then, numerous other antifolates have been used to treat a wide range of infections. Antifolates, such as methotrexate, are potent anticancer agents and antivitamin K, such as warfarin, are used as anticoagulants. Despite several years of research, most antivitamin-based drugs are limited to vitamin K and B9, and the development of antagonists for other vitamins is still in the nascent stage. In the era of antimicrobial resistance, antivitamins can be considered as a promising alternative to develop newer antimicrobials and are worth exploring further. This review discusses key antivitamins at different stages of development which have potential utility as antibiotic drug candidates. The summary of studies of antivitamins in clinical development is also narrated.

Keywords

Antivitamins, Antimicrobials, Antifolates

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Introduction

Antivitamins are the compounds that hamper the essential effects of vitamins. Based on their mode of action, antivitamins are broadly divided into two classes: Class A and B. Class A antivitamins are inhibitors whereas the class B are structural modifiers.[1]

Antivitamins hold countless medicinal applications. Over the years, a wide array of drugs has been developed from antivitamins ranging from anticoagulants to anticancer drugs. Prontosil, the first commercially available antimicrobial agent for humans, is a B_9 antivitamin.[1,2] Another important example of antivitamins is the anticoagulant warfarin, an antivitamin K.[1]

Antivitamins are attractive antimicrobials for several reasons. First, many microorganisms have vitamin transporters, making the delivery of the vitamin analogs to the target molecules very efficient. Second, vitamin analogs act on multiple cellular targets, thus reducing the odds of resistance development.[3]

Excessive and unnecessary usage of antibiotics has led to the ever-growing menace of antibiotic resistance. To overcome the rising army of antibiotic-resistant organisms, novel antibiotics are required; and the antivitamins are promising candidates. Despite the tremendous potential of antivitamins as antibiotics, this area of research is considerably unexplored. In this review, we discuss the potential antivitamins B_1, B_2, B_9, and B_{12} and their antimicrobial actions.

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Thiamine (B_1) Antivitamins

Vitamin B_1, thiamine, is a crucial vitamin for the maintenance of metabolic functions of most living organisms. Thiamine diphosphate (ThDP) acts as a coenzyme for several enzymes, such as oxoglutarate ferredoxin oxidoreductase, 2-oxoglutarate dehydrogenase, oxalate oxidoreductase, pyruvate ferredoxin oxidoreductase, pyruvate dehydrogenase, pyruvate oxidase, dihydroxyacetone synthase, transketolase, 1-deoxy-D-xylulose 5-phosphate synthase, phosphoketolase, pyruvate decarboxylase, and indolepyruvate decarboxylase, in prokaryotes involving carbohydrate, lipid, and amino acid metabolism (Figure 1). Furthermore, bacteria, fungi, and plants possess the de novo pathways for biosynthesis of ThDP or thiamine pyrophosphate (TPP) unlike mammals.[4]

Thiamine antivitamins were first developed to induce thiamine deficiency in experimental models.[5,6] Nowadays, they show great prospect in the field of medicine. Some examples of synthetic thiamine antivitamins include oxythiamine, amprolium, pyrithiamine, and 3-deazathiamine.[6] Recently, a natural antivitamin of thiamine was discovered known as 2′-methoxy-thiamine[7] (Figure 1). The biosynthesis of TPP has been an appealing target for developing antibiotics against bacteria. The *Pseudomonas aeruginosa* thiamine monophosphate kinase (PaThiL) is a pivotal enzyme at last step of biosynthesis of TPP. Furthermore, it is demonstrated that noncompetitive inhibition of PaThiL by WAY213613 exhibits potent action against *P. aeruginosa*.[8] This biosynthesis pathway involving ThiL is also found in other bacteria such as *Salmonella typhimurium* and *Escherichia coli*. However, in fungi, such as *Saccharomyces cerevisiae*, synthesis of TPP occurs from thiamine through thiamine pyrophosphokinase[9] (Figure 2).

Oxythiamine, pyrithiamine, and 3-deazathiamine inactivate ThDP-dependent enzymes. In addition, pyrithiamine may also impede conversion of thiamine to ThDP by inhibiting the enzyme thiamine pyrophosphokinase. Moreover, action of oxythiamine and pyrithiamine on microbes and fungi is further mediated by action on riboswitches.[6,10] Amprolium exhibits antivitamin action by preventing thiamine uptake.[11] The potential applications of each of these thiamine antivitamins are discussed.

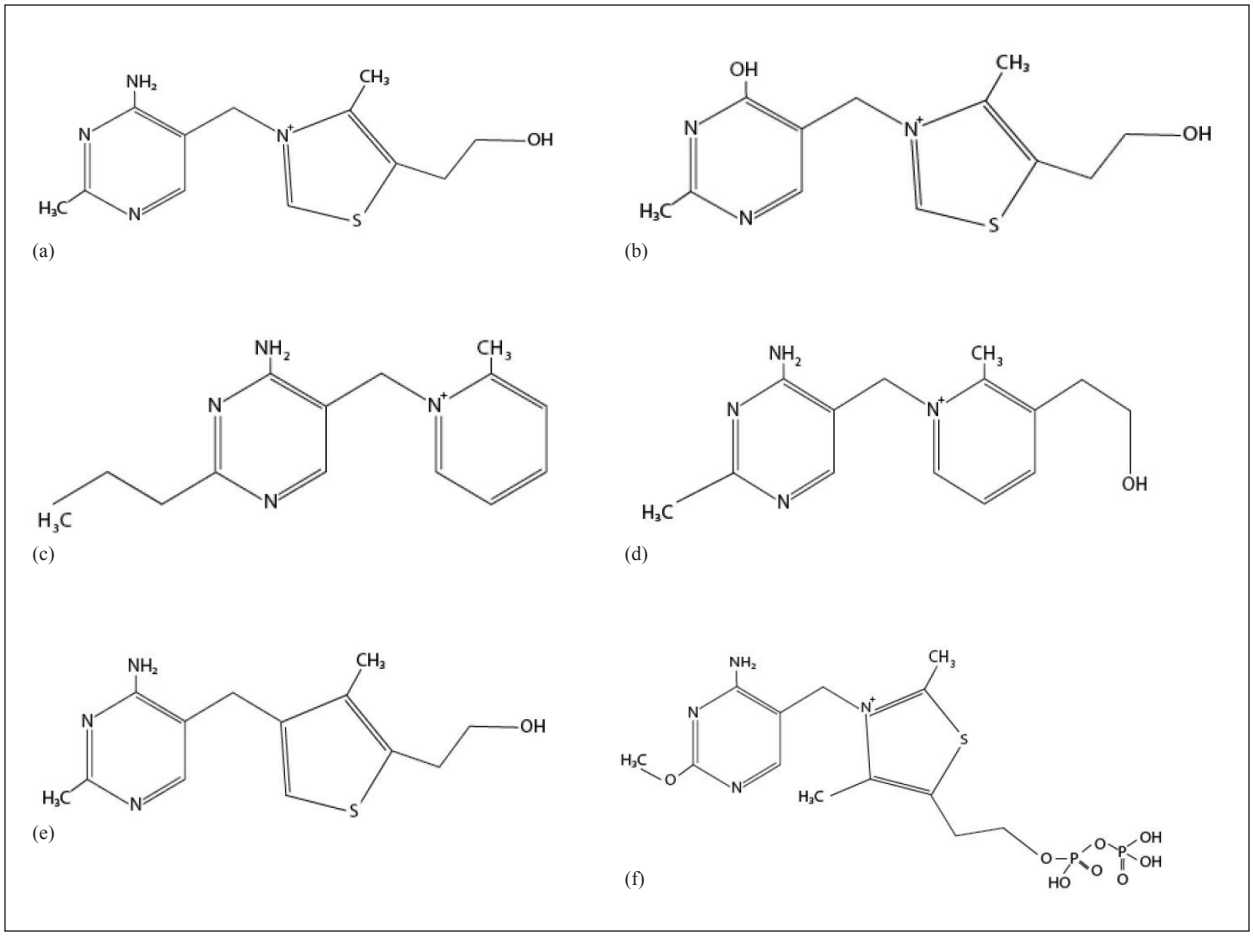

Figure 1. (a) Thiamine, **(b)** Oxythiamine, **(c)** Amprolium, **(d)** Pyrithiamine, **(e)** 3-Deazathiamine, and **(f)** 2′-Methoxy-Thiamine.

Source: Modified and adopted from Tylicki et al.[6] and Rabe von Pappenheim et al.[7]

Oxythiamine

Oxythiamine is shown to inhibit the growth of malarial parasite *Plasmodium falciparum* by acting on a thiamine-related pathway.[12] It also reduces proliferation of yeast, such as *S. cerevisiae*.[13,14] It could act synergistically with ketoconazole to reduce fungal growth especially those of the genus *Malassezia*. Hence, this antithiamine can be considered for being a supportive agent in superficial mycoses treatment.[13] Similarly, oxythiamine also confers resistance to Lansing strain of poliomyelitis virus in mice, shedding light on its potential as an antiviral agent which needs to be explored further.[15] In addition, oxythiamine shows interesting antitumor properties. It inhibits cell proliferation in MIA pancreatic carcinoma lines and Ehrlich's tumor and demonstrates antimetastatic effect against Lewis lung carcinoma. Moreover, when combined with other anticancer agents, it is effective against drug-resistant colon adrenocarcinoma and chronic myeloid leukemia.[6,16] Thus, it is a promising drug candidate with potential in targeted therapies.

Amprolium

Amprolium is widely used in the treatment of coccidiosis in cattle and poultry.[6,17] It has also been used in humans for treatment of severe coccidiosis in acquired immunodeficiency syndrome (AIDS) patients unresponsive to standard treatment.[18]

Pyrithiamine

Pyrithiamine, when given in small doses, inhibits growth of fungi and bacteria. It is used to induce thiamine deficiency in experimental conditions[6] (Figure 2).

2′-Methoxy-Thiamine

2′-methoxy-thiamine (MTh) is a naturally occurring antivitamin B_1 derived from bacimethrin.[19] It inhibits ThDP-dependent enzymes of bacteria. It shows differential effects on human and bacterial enzymes, with no inhibitory effects on the former.[20]

Thiamine antivitamins can be considered as useful agents in the treatment of fungal and bacterial infections as well as cancer. However, exposure to trace amounts of B_1 antivitamins in food can adversely affect metabolism. Thus, there is a need to develop new methods to detect these trace amounts in our diet and environment and study the effects of such contamination on our health.[20]

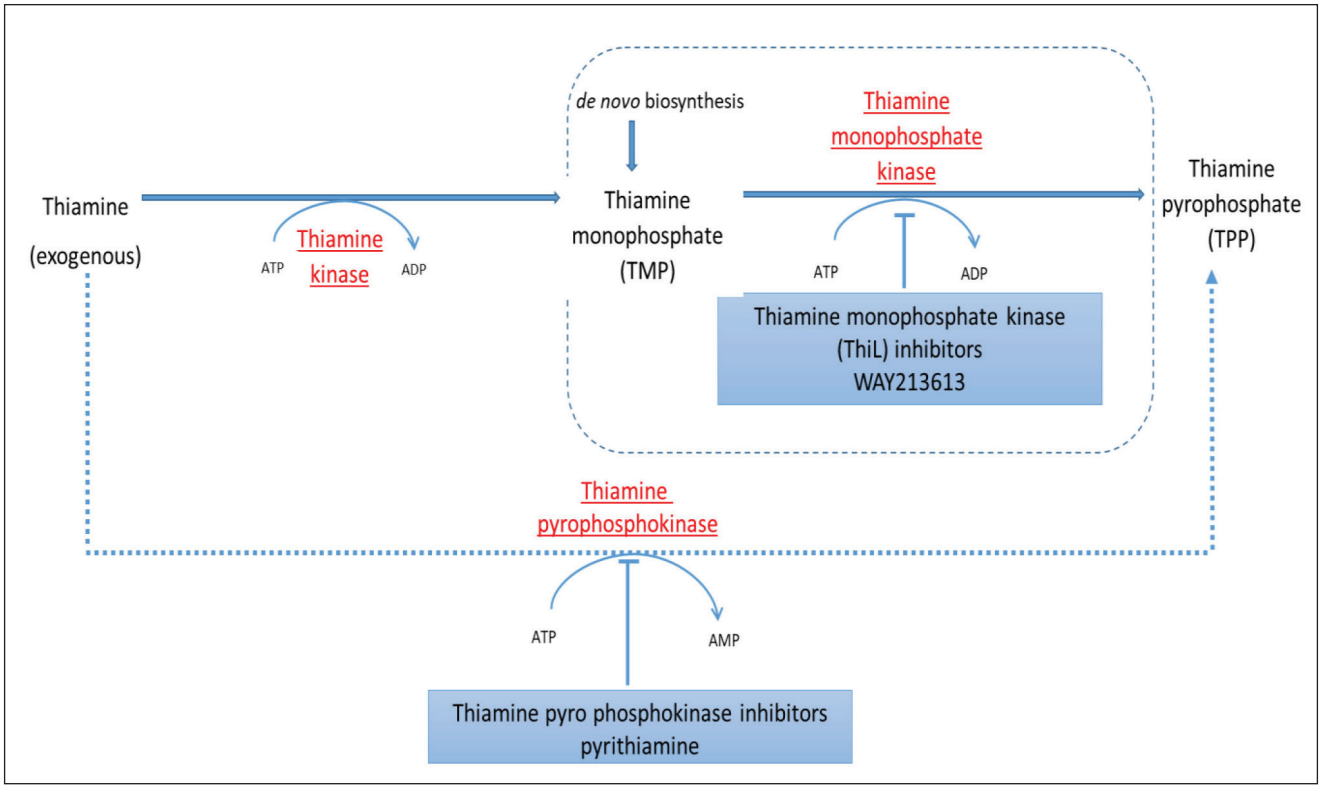

Figure 2. Thiamine Pathway and Key Enzymes. Dotted Box Shows Pathway Exclusive to Bacteria Such as *E. coli* and *S. typhimurium*. The Dotted Arrow Represent Pathway in *S. cerevisiae*.

Source: Modified and adopted from Kim et al.[8] and Webb et al.[9]

Riboflavin (B_2) Antivitamins

Riboflavin, vitamin B_2, is a direct precursor for the cofactors flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which carry out a wide range of biochemical functions.[3] Riboflavin antivitamins can be divided into natural and synthetic agents.

Natural Riboflavin Antivitamins

Cofactor F420, molybdopterins, roseoflavin (RoF), and 8-demethyl-8-amino-riboflavin (AF) are natural riboflavin analogs.[21,22] RoF and AF are the only natural antivitamins B_2 with antibiotic action.[22] Both of them are synthesized by *Streptomyces davawensis*. They demonstrate antimicrobial action not only against gram-positive bacteria, such as *Bacillus subtilis*, but also against gram-negative bacteria if uptake systems for flavins/flavin analogs are present.[3,23,24] Both RoF and AF inhibit flavoenzymes and block the FMN riboswitch, ultimately resulting in riboflavin deficiency. In addition, RoF also shows antioncogenic potential. One study has demonstrated an economical method for the large-scale production of RoF.[25] Natural B_2 antivitamins have a few disadvantages. A single mutation in *ribG* FMN riboswitch or in the flavokinase/FAD synthetase gene *ribC* can result in resistance to RoF.[26] Also, the adverse effects of natural riboflavin antivitamins on human metabolism cannot be dismissed.[22] AF is less toxic for humans than RoF making it a better alternative for the development of novel antibiotics.[3]

Synthetic Riboflavin Antivitamins

The synthetic RF analogs isoriboflavin (5, 6-dimethyl-9-Dribitylisoalloxazine), dichloroflavin and galactoflavin effectively inhibit the growth of various organisms by inhibition of flavoenzymes. However, the in vivo toxicity of these synthetic antivitamins overrides their use as antibiotics.[3]

Folate (B_9) Antivitamins

Folate plays an essential role in the synthesis of DNA, RNA, and amino acids. Folate antivitamins, also known as antifolates, are classified into two groups: classical antifolates and nonclassical antifolates. Classical antifolates are structural analogs of folic acid whereas nonclassical antifolates are structurally dissimilar compounds.[27] Antifolates have three

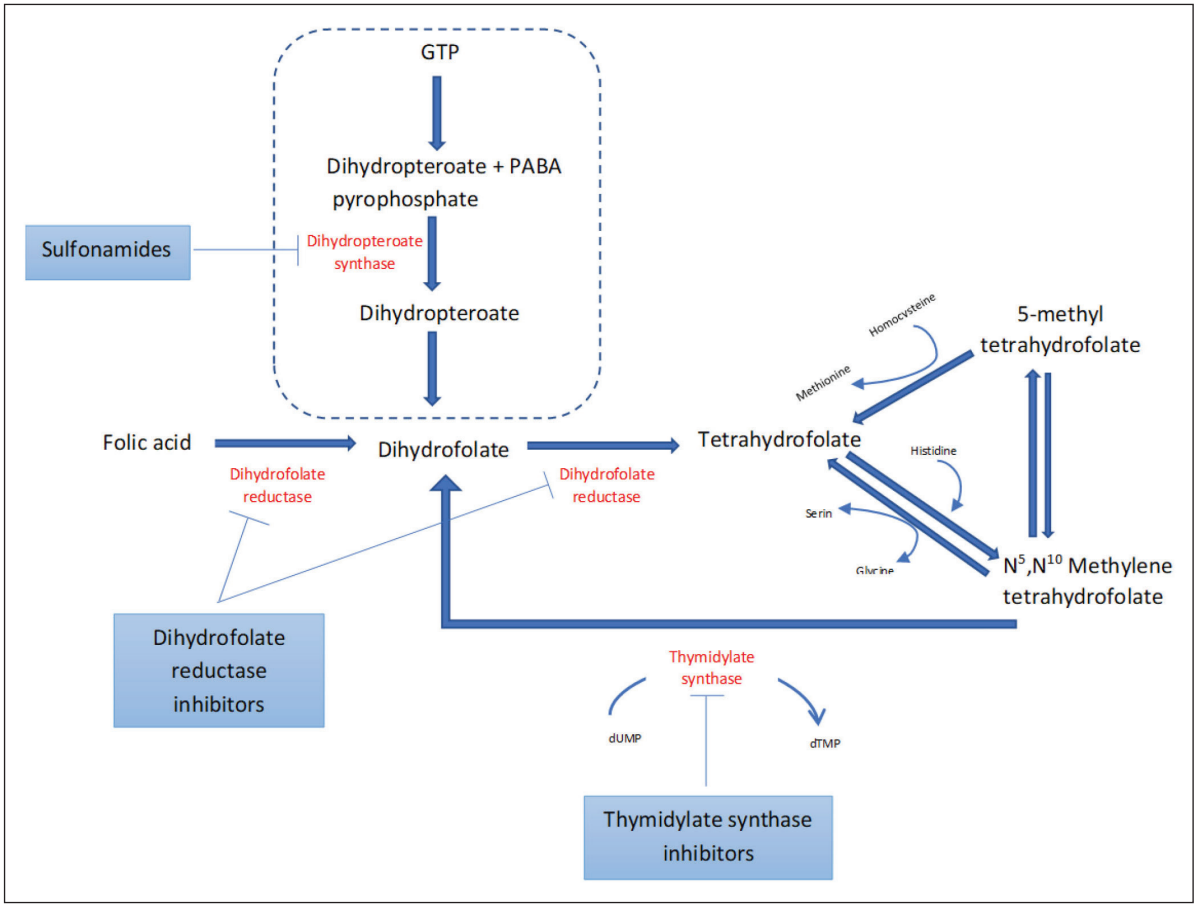

Figure 3. Folate Cycle and Key Enzymes Targeted by Antifolates. Dotted Box Shows Pathway Exclusive to Bacteria.

Source: Modified and adopted from Fernandez-Villa et al.[28]

mechanisms of action: (a) inhibition of folic acid biosynthesis, (b) hindering cellular uptake, and (c) prevention of folate-dependent enzymatic processes (Figure 3).

Since their discovery in 1930s, antifolates have been widely used as antibacterial, antiprotozoal, and anticancer agents (Table 1). Sulfonamides such as sulfadiazine and dapsone are extensively used as antibiotics. They inhibit dihydropteroate synthase (DHPS), an enzyme specific to bacteria. Dihydrofolate reductase (DHFR) inhitors such as proguanil and pyrimethamine are potent antimalarial agents.[28] Another prominent antivitamin B_9 is methotrexate, an anticancer agent. Recently, methotrexate has been proven to be an effective antifungal drug as well, inhibiting growth of *Candida albicans*.[29] In recent years, excessive use of antifolates has led the way to the development of antibiotic resistance. Thus, newer antifolates have been produced to tackle this problem, which are discussed here.

Iclaprim

Iclaprim is a novel highly potent inhibitor of dihydrofolate reductase (DHFR) developed to overcome resistance to trimethoprim (TMP). It demonstrates antibacterial activity against gram-positive bacteria such as Methicillin Resistant *Staphylococcus aureus* (MRSA) TMP-resistant MRSA, *Streptococcus pyogenes*, in addition to gram-negative bacteria such as *Enterococcus* and *Haemophilus influenzae*. The odds of resistance developing to this drug are also reported to be low because it is 20 times more potent in inhibiting DHFR.[31] It is a favorable candidate for the treatment of bacterial skin and soft-tissue infections. Iclaprim showed promising results in clinical trials, when compared with vancomycin and linezolid[2,28,32] (Table 2).

Propargyl-Linked Antifolates

The propargyl-linked antifolates (PLA) are an upcoming class of drugs designed to target both TMP-sensitive and TMP-resistant organisms. These compounds are found to be effective against both gram-positive and gram-negative bacteria, including multidrug-resistant *Staphylococcus aureus*.[38,39] In addition, PLAs also inhibit *Mycobacterium tuberculosis*, with two compounds being very potent inhibitors of multi-drug resistant (MDR) and extensively drug resistant (XDR) strains as well.[38] The PLAs have low frequency of inducing resistant mutations.[39]

Abyssomicins

Abyssomicins are antifolates that inhibit the para aminobenzoic acid (PABA) synthesis in the chorismate pathway. They are class I spirotetronate polyketides belonging to the class of tetronate antibiotics. Not only do the drugs inhibit mycobacteria and gram-positive bacteria but they also demonstrate action against latent HIV reactivation and antitumor activities.[40] Abyssomicins selectively inhibit the enzyme 4-amino-4-deoxychorismate synthase which catalyzes the transformation of chorismate to PABA, an intermediate in the folic acid pathway.[41]

Table 1. Antibiotic Antifolates Currently in Clinical Application[30]

Drug	Category	Mechanism of Action	Indication
Mafenide	Antibiotic	Unknown	Burn wounds
Silver sulfadiazine	Antibiotic	DHPS inhibitor, silver biocide effect	Second- and third-degree burns
Sulfadiazine	Antibiotic	DHPS inhibitor	Rheumatic fever, meningococcal meningitis, urinary tract infections, trachoma, chancroid
Sulfacetamide	Antibiotic	DHPS inhibitor	Bacterial vaginitis, keratitis, acute conjunctivitis, blepharitis
Sulfisoxazole	Antibiotic	DHPS inhibitor	Urinary tract infections, meningococcal meningitis, acute otitis media, trachoma, inclusion conjunctivitis, nocardiosis, chancroid, toxoplasmosis
Dapsone	Antibiotic	DHPS inhibitor	Leprosy and dermatitis herpetiformis
Proguanil	Antimalarial	DHFR inhibitor	Prevention and suppression of malaria caused by susceptible strains of P. falciparum and other species of Plasmodium
Pyrimethamine	Antiparasitic	DHFR inhibitor	Treatment of toxoplasmosis and acute malaria; for the prevention of malaria in areas nonresistant to pyrimethamine
Sulfadoxine + pyrimethamine	Antimalarial	DHPS and DHFR inhibitor	As combination for the treatment or prevention *Plasmodium falciparum* malaria with chloroquine resistance
Sulfamethoxazole + trimethoprim	Antibiotic	DHPS and DHFR sequential inhibitor	As a combination in urinary tract infections, acute otitis media, acute exacerbations of chronic bronchitis, shigellosis, *Pneumocystis jiroveci* pneumonia, and enterotoxigenic *E. coli* induced travelers' diarrhea

Abbreviations: DHPS, dihydropteroate synthase; DHFR, dihydrofolate reductase.

Table 2. The Characteristic Features of the Key Clinical Trials of Iclaprim

Study	Phase	Study Design	Population	Study Arms		Number of Subjects	Primary Outcome	Results	References
				Experimental	Comparator				
A phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of intravenous iclaprim versus vancomycin in the treatment of ABSSSI: REVIVE-1	Phase 3	Randomized, double-blind controlled study	Acute bacterial skin and skin structure infections	Iclaprim 80 mg intravenous every 12 h for 5 to 14 days (*n* = 298)	Vancomycin 15 mg/kg intravenous every 12, 24 or 48 h based on creatinine clearance; 5 to14 days (*n* = 300)	598 (intention to treat)	≥20% reduction in lesion size at 48 to 72 h compared to baseline in all randomized patient	Iclaprim noninferior to vancomycin at primary end point of early clinical response (iclaprim 80.9% [241/298] compared with vancomycin 81.0% [243/300])	33,34
A phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of intravenous iclaprim versus vancomycin in the treatment of ABSSSI: REVIVE-2	Phase 3	Randomized, double-blind controlled study	Acute bacterial skin and skin structure infections	Iclaprim 80 mg intravenous every 12 h for 5 to 14 days (*n* = 295)	Vancomycin 15 mg/kg intravenous every 12, 24, or 48 h based on creatinine clearance; 5-14 days (*n* = 305)	600 (intention to treat)	Percent of participants with ≥20% reduction in lesion size at 48 to 72 h compared to baseline	Iclaprim noninferior to vancomycin at primary end point of early clinical response (iclaprim 78.3% [231/295] compared with vancomycin 76.7% [234/305])	34
Phase 3, randomized, investigator-blind, multicenter study to evaluate efficacy and safety of intravenous iclaprim vs. linezolid in complicated skin and skin structure infections (ASSIST-1)	Phase 3	Randomized double blind controlled study	Complicated skin and skin structure infection	Iclaprim 0.8 mg/kg; 30-min iv. infusion every 12 h for 10 to 14 days (*n* = 250)	Linezolid 600 mg 30-min iv. infusion every 12 h for 10 to 14 days (*n* = 247)	497 (intention to treat)	Clinical cure rate (the ratio of number of clinically cured patients to the total number of patients in the population) at 7 to 14 days after the end of therapy	Iclaprim clinical effect comparable to linezolid at test of cure (treatment difference, –5.6%; (95% CI [11.72, 0.6])	[35]

(*Table 2 continued*)

(*Table 2 continued*)

Study	Phase	Study Design	Population	Study Arms		Number of Subjects	Primary Outcome	Results	References
				Experimental	Comparator				
Phase 3, randomized, investigator-blind, multi-center study to evaluate efficacy and safety of intravenous iclaprim versus linezolid in complicated skin and skin structure infections (ASSIST-2)	Phase 3	Randomized double blind controlled study	Complicated skin and skin structure infection	Iclaprim 0.8 mg/kg; 30-min iv. infusion every 12 h for 10 to 14 days (*n* = 250)	Linezolid 600 mg 30-min iv. infusion every 12 h for 10 to 14 days (*n* = 244)	494 (intention to treat)	Clinical cure rate (the ratio of number of clinically cured patients to the total number of patients in the population) at 7 to 14 days after the end of therapy	Iclaprim clinical cure (iclaprim 81.3% [204/251]) noninferior to linezolid (81.9% [199/243]) at test of cure (treatment difference, –0.6%; (95% CI [7.7, 6.5]).	[36]
Randomized, double-blind, multicenter study to evaluate efficacy and safety of intravenous iclaprim versus vancomycin in the treatment of hospital-acquired, ventilator-associated, or health Care associated pneumonia suspected or confirmed to be because of gram-positive pathogens	Phase 2	Randomized double blind controlled study	Hospital-acquired pneumonia Ventilator-associated pneumonia Healthcare-associated pneumonia	Iclaprim 0.8 mg/kg q12h for 10 to 14 days; iclaprim 1.2 mg/kg q8h for 10 to 14 days (*n* = 47)	Vancomycin 1 g q12h for 7 to 14 days (*n* = 23)	70	Efficacy: Clinical cure rate comparison of the two iclaprim dosing regimens vs. vancomycin [Time Frame: at test of cure (TOC) visit] Efficacy: Iclaprim clinical cure rates [time frame: at TOC and end of therapy (EOT)]	Iclaprim comparable to vancomycin at clinical cure at test of cure (iclaprim q12h 73.9% [17/23], iclaprim q8h 62.5% [15/24], vancomycin 1 g 52.2% [12/23]. Iclaprim comparable to vancomycin at day 28 mortality (iclaprim q12h 8.7% [2/23], iclaprim q8h 12.5% [3/24], vancomycin 1 g 21.7% [5/23])	[37]

4′-Desmethyltrimethoprim (4′-DTMP)

Recently, a derivative of TMP called 4′-desmethyltrimethoprim (4′-DTMP) was identified to overcome antibiotic resistance to TMP. The 4′-DTMP is more effective than TMP against mutant strains of *E. coli* and exhibits antibiotic action similar to TMP against several gram-negative and gram-positive species. Moreover, it confers mutations at a markedly slower rate as compared to TMP and hampers the development of resistant mutations.[42]

Novel DHPS Inhibitors

Novel inhibitors of the DHPS enzyme are currently being explored as alternate antifolates. Pterin–sulfonamides conjugates, pterin site inhibitors, and pterin/pABA site binders are some of the compounds being studied.[28,43]

Cobalamin (B12) Antivitamins

Vitamin B_{12} is a cofactor in DNA synthesis and contributes to the normal functioning of the nervous system and the maturation of red blood cells. Antivitamins B_{12} are metabolically inert cobalamins (Cbls) with molecular structures resembling vitamin B_{12} (CNCbl or AdoCbl) that induce "functional" B_{12} deficiency.[44,45] Examples are the aryl-cobalamins such as 4-ethylphenyl-cobalamin (EtPhCbl). A limitation of EtPhCbl is its light sensitivity; exposure to light converts EtPhCbl into Cbls which are precursors for the B_{12}-cofactors, thus branding them as "conditional antivitamins" whose effects can be reversed by irradiation. Recently, a group of light-stable antivitamins called as organometallic alkynyl-Cbls (e.g., 2-phenyl-ethynyl-cobalamin, PhEtyCbl) was created in order to overcome the limitation of EtPhCbl.[44,46]

Antivitamins B_{12} inhibit vitamin B_{12}-dependent enzymes by reducing synthesis and availability of B_{12} cofactors, thus impairing growth of bacteria.[44,45,47,48] They also impair the uptake of essential B_{12} derivatives by B_{12}-dependent microorganisms. Antivitamins B_{12} enhance the antibiotic action of sulfonamides when added to the latter.[48] Thus, antivitamins B_{12} show great promise as novel antibiotics. Moreover, they also show potential as anticancer agents.[1]

Despite tremendous efforts, not a single antivitamin B_{12} has reached clinical trials. Thus, there is a long road ahead in the development of antivitamins B_{12} for medical applications.

Declaration of Conflicting Interests

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