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Editorial

Newer Tetracyclines. Are they Different or the Same Old News?

Elizabeth Awudi[1], Kyle Fischer[1] and Salim Surani[2]*

[1]Bay Area Medical Center, Corpus Christi, Texas, USA

[2]Adjunct Clinical Professor, Texas A&M University, College Station, Texas, USA

***Corresponding Author:** Salim Surani, Adjunct Clinical Professor, Texas A&M University, College Station, Texas, USA.

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Tetracyclines have been one of the first antibiotics in use to treat infections and has been in our armamentarium for decades. Tetracyclines are a class of antibiotics that has effect on wide variety of bacterial infections stemming from both gram-positive and gram-negative bacteria as well as for prophylaxis against bacteria that could possibly be used in biological weapons [1]. There have been several newly approved agents in the tetracycline class, leading healthcare providers to deliberate the efficacy and safety of Omadacycline, Eravacycline, and Sarecycline.

Omadacycline at the moment is one of the newest and more popular approved agents of the tetracycline class. This agent is available as an oral option and parenteral option with once a day dosing for the treatment of acute bacterial skin and skin-structure infections as well as community-acquired bacterial pneumonia. Omadacycline has proven to have a powerful *in vitro* activity against methicillin-resistant Staphylococcus aureus (MRSA) but fails to show activity against *Pseudomonas aeruginosa*. Upon reviewing two phase 3, double-blind, randomized clinical trials, the data has shown Omadacycline to be noninferior to linezolid for the treatment of acute bacterial skin and skin-structure infections (ABSSSI) and noninferior to moxifloxacin for the treatment of CABP [1,2]. The exclusion of previous antibacterial therapy when treating ABSSI and limiting it to only 25% of the patients for the treatment of community-acquired bacterial pneumonia instills a sense of reassurance that the treatment effect was relevant. Additionally, Omadacycline has shown activity against typical respiratory pathogens as well as atypical organisms such as *Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydia pneumoniae*. These atypical organisms have eluded beta-lactam antibiotics, so this is a promising role and benefit. This new agent also provides activity against organisms expressing tetracycline efflux and ribosomal protection, which is the cause of tetracycline antibiotic resistance, making it a newer generation tetracyclines and differentiating them from the older tetracyclines. The activity of Omadacycline is several times than its counterparts of minocycline and doxycycline against Enterobacteriaceae and *Acinetobacter baumannii*. The minimum inhibitory concentrations are less than or equal to 4 ug per milliliter for 90% of strains [3]. The most common adverse effects that have been reported to date are gastrointestinal upset, elevated liver function tests, hypertension, diarrhea, headache, and infusion site reactions. The pharmacokinetics of this agent has shown that if taken with food, cation-containing agents, and dairy products absorption will decrease. There has also been data showing that concomitant use with anticoagulants will increase the effects of the latter [4].

An additional novel tetracycline antibiotic is Sarecycline. Sarecycline is indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients nine years of age and older. This antibiotic has shown to display a narrow spectrum of antimicrobial activity that can possibly lead to less antibiotic resistance. There is also some speculation that Sarecycline should lead to a decrease in gastrointestinal distress due to the limited activity against enteric gram-negative organisms [5,6]. This is a very promising action of Sarecycline, as treating acne vulgaris with traditional tetracyclines like doxycycline have been associated with increase gastrointestinal tract side effects and disruption of the gut microbiome. There are still several challenges like resistance among the C. acnes isolates, but the activity of this new tetracycline may aid in in the reduction of to its antibiotic resistance. The absorption of this drug has also been noted to decrease when taking with high-calorie meals, meals high in fat, and dairy products. The pharmacokinetic profile of Sarecycline has also led to the conclusion that no dose adjustments for hepatic or renal impairment is necessary [6].

The final novel tetracycline is Eravacycline, which is administered intravenously for the treatment of intra-abdominal infections in adults. This new tetracycline has showed similar cure rates to that of carbapenems and has also showed efficacy against carbapenem resistant *Acinetobacter baumannii*. In the IGNITE4, randomized, multicenter, prospective trial that compared Eravacycline versus meropenem in the treatment of complicated intra-abdominal infections, results showed that treatment with Eravacycline was noninferior to meropenem in adult patients. These results also included infections caused by resistant pathogens and the main adverse effect that was noted was that of nausea and vomiting [7]. Furthermore, besides the label indication to treat complicated intra-abdominal infections, Eravacycline had the potential to be indicated for the treatment of complicated urinary tract infections. This indication ended up not coming to fruition due to the failed phase 3 trials that evaluated the use of Eravacycline in complicated urinary tract infections, thus it is not indicated for treatment [7,8]. Table 1 Illustrates the indication, efficacy, dosing, pharmacokinetics, pharmacodynamic and adverse effects of these drugs.

Drug	**Eravacycline**	**Sarecycline**	**Omadacyline**
Route	IV	PO	PO & IV
Indication	-Treats intra-abdominal infections in adults caused by Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Enterobacter cloacae, Klebsiella oxytoca, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Streptococcus anginosus group, Clostridium perfringens, Bacteroides species, and Parabacteroides distasonis [8].	-Approved for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients that are 9 years old and above [5].	-Indicated for the treatment of adults with community-acquired bacterial pneumonia caused by *S. pneumoniae, S. aureus* (methicillin-susceptible isolates), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, and Chalmydophila pneumoniae.* -This medication is also used to treat acute bacterial skin and skin structure infections caused by *S. aureus, Staphylococcus lugdunesis, Streptococcus pyogenes, Streptococcus anginosus group, Enterococcus faecalis, Enterobacter cloacae, and K. pneumoniaee*
Efficacy	-Eravacycline showed similar clinical cure rates as carbapenems for the indication above and it also has shown to have activity against carbapenem resistant *Acinetobacter baumannii.*[8]	-Sarecycline has a narrow spectrum of antimicrobial activity, so it should be less likely to contribute to antibiotic resistance. It also showed enhanced GI tolerability due to the limited activity against gram (+) organisms [6].	-Clinical data has shown that omadacycline is as effective as linezolid for these indications [4].
Dosing	Intra-abdominal infections: IV: 1 mg/kg every 12 hours for 4 to 14 days Dosage adjustment with concomitant strong CYP3A inducers: Increase to 1.5 mg/kg every 12 hours -NO dosing adjustment for hepatic impairment -NO dosing adjustment for mild to moderate renal impairment -Adjust dose to 1 mg/kg every 12 hours, then 1 mg/kg every 24 hours for severe renal impairment [8].	-33 to 54 kg: 60 mg QDaily -55 to 84 kg: 100 mg QDaily -85 to 136 kg: 150 mg QDaily -NO dose adjustments for hepatic/renal impairment [5]	-Pneumonia, community acquired: Loading dose: IV 200 mg QDaily. Maintenance dose: IV 100 mg QDaily or Oral: 300 mg QDaily - - Duration of Therapy: 7 to 14 days -Skin and skin structure infections: Loading dose: IV: 200 mg QDaily or Oral: 450 mg QDaily on days 1 and 2. Maintenance dose: IV: 100 mg QDaily or Oral: 300 mg QDaily. Duration of Therapy: 7 to 14 days -NO hepatic/renal adjustment [4].

Pharmacodynamics/ Pharmacokinetics	-Protein binding: 79% to 90% Metabolism: Primarily by CYP3A4 and FMO-mediated oxidation -Half-life elimination: 20 hours Excretion: Urine: 34% (20% as unchanged drug); Feces 47% (17% as unchanged drug) [8].	-Protein binding: 62.5 % to 74.7% -Half-life elimination: 21 22 hours -Time to peak: 1.5 to 2 hours; delayed by 0.53 hour when administered with high-fat, high calorie meal that includes milk Excretion: Feces (42.6%; 14.9% as unchanged drug) Urine (44.1%, 24.7% as unchanged drug)[5]	-Absorption: food decreases rate and extent of absorption -Protein binding: 20% -Bioavailability: 34.5% following a single 300 mg dose -Half-life elimination: IV: 16 hours; Oral: 13.45 to 16.83 hours -Time to peak: IV: 0.5 hours; Oral: 2.5 hours -Excretion: IV: Urine (27% as unchanged drug) Oral: Feces: (77.5% to 84%) Urine: 14.4% [4].
Adverse Events	-Most common adverse events deal with GI symptoms. -Adverse reactions and C.I. are similar to the tetracycline class.	-Most common is Nausea followed by headache and nasopharyngitis. The S.E. common to the tetracycline class of antibiotics are also noted.	-Most common adverse events deal with GI symptoms -Adverse reactions and C.I. are similar to the tetracycline class.

Table 1: Indication, efficacy, pharmacokinetics, pharmacodynamic and adverse effects of the newer tetracyclines.

In Conclusion, these newer tetracyclines offers hope in the treatment of complex and resistant infection at the same time differentiating themselves from the older tetracyclines based on the indication, resistance and safety profile. Phase 4 and market data in future may decide the fate of these drugs, if they hold to their promise.

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