Research and Development of the Novel Quinolone Antibacterial Agents: Ofloxacin, Levofloxacin, and Sitafloxacin

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The quinolone antibacterial agents originated from nalidixic acid (NA), which was developed in the USA in 1962. NA was used for the treatment of regional infections, e.g., urinary tract infections (UTIs); it was notable for its novel mode of action and its effectiveness when given orally. Consequently, numerous research groups began to search more effective quinolones for the treatment of various infections, including respiratory tract infections (RTIs), but even by the end of the 1970s this goal was still a long way from being realized.

By the mid 1970s, we had already found several potent acidic quinolones, the so-called "old quinolones". Among these, DJ-6783, which showed high blood concentrations in humans, was selected as a candidate in 1978, but the development of this compound was discontinued because of unexpectedly efficacy in RTIs. About the same time, the first new quinolone, norfloxacin (NFLX), was tested in a clinical study and showed efficacy against RTIs in humans despite insufficient blood concentrations. NFLX is zwitterionic, making it markedly different from the old quinolones in terms of activity and pharmacokinetics; for example, it has favorable penetration into the tissues, giving it high clinical efficacy. These facts encouraged us to develop more effective new quinolones, and we finally found ofloxacin (OFLX, Tarivid®). OFLX had a broad spectrum of antibacterial activity and was effective against UTIs and RTIs.

OFLX was superior to oral β-lactam antibiotics for the treatment of these infections. OFLX is characterized by a pyridobenzoxazine pharmacophore and has an asymmetric carbon atom at the C_3 position. By technological advancements in chiral separation using chromatography, we finally succeeded in providing a chiral compound, the (3*S*)-enantiomer (levofloxacin) of OFLX. Levofloxacin (LVFX, Cravit®) was found to have favorable properties over OFLX. LVFX is the first optically active fluoroquinolone, and the success of its development created a new trend in the chiral switch of drugs approved as racemates. Since its launch in 1993, LVFX has been administered to more than 600 million patients. LVFX is clinically recognized to be a powerful and safe weapon for the treatment of various bacterial infections and has become a blockbuster drug, with annual sales of around 3 billion dollars worldwide.

The new quinolones have been a highly successful class of antibacterials, but the early ones have limited potency against quinolone-resistant bacteria. This led us to the development of newer, potent quinolones. Initially, we assessed the SAR, physicochemical properties, pharmacokinetics, and toxicological profiles of various quinolone compounds. Among these factors, lipophilicity (i.e., the partition coefficient) was adopted as an important factor for predicting a compound's pharmacological properties. Through several serendipitous findings, sitafloxacin (STFX, Gracevit®), which has a unique N_1-2-fluorocyclopropyl group, was discovered. STFX has both potent activity against a number of LVFX-resistant bacteria and favorable lipophilicity. This next-generation new quinolone is characterized by high therapeutic efficacy and a good safety profile in the treatment of UTIs and RTIs. It was launched in Japan in 2008.