exposure, tularemia due to *Francisella tularensis*, and plague due to *Yersinia pestis* (Mansour et al. 2013). Fidaxomicin, the 18-membered ring macrolide, has minimal systemic absorption and is used in the treatment of *Clostridium difficile* (Venugopal and Johnson 2012).

Apart from their antibacterial uses, macrolides can also be used to treat some parasitic and fungal infections. Azithromycin is active against *Plasmodium falciparum* and *Plasmodium vivax* and can be an effective antimalarial treatment, especially when used in conjunction with other antimalarial drugs in the context of pregnant women with malaria, as well as being used in a liposomal preparation topically for the treatment of cutaneous leishmaniasis (Nakornchai and Konthiang 2006; Phong et al. 2016; Rajabi et al. 2016). Roxithromycin is used in the treatment of amoeboid infections caused by *Acanthamoeba castellanii* (Mattana et al. 2004). Polyene antimycotics are a subclass of macrolides, which include amphotericin B and nystatin A1, which are used clinically for their antifungal activity. This activity is mediated through binding to ergosterol in fungal cell membranes, causing ion leakage of potassium and sodium (Mesa-Arango et al. 2012).

Completely apart from their antimicrobial activity, macrolides such as tacrolimus, pimecrolimus, and rapamycin/sirolimus additionally can be used as immunosuppressants in the context of organ transplants and immune disorders. Tacrolimus therapy shows efficacy in rheumatoid arthritis and can also be used to treat cyclosporine A-resistant or cyclosporine A-dependent minimal change disease as well as vernal keratoconjunctivitis (Chatterjee and Agrawal 2016; Kitahara and Kawai 2007; Xu et al. 2017). Rapamycin blocks the mTOR signaling pathway and can be used alone or in conjunction with tacrolimus to provide steroid-free immunosuppression (Asante-Korang et al. 2017).

5.5 Next-Generation Macrolides and Future Use

Continuing to address the bacterial evolution of antibiotic resistance necessitates the development of novel antibiotics. The development of novel macrolides, however, in recent years has encountered a number of stumbling blocks. Concerns over the ketolides, specifically with respect to telithromycin and its associated hepatotoxicity, led many companies to halt development of ketolides (Fernandes et al. 2017; Georgopapadakou 2014). While having gained orphan drug status for some prophylactic use, cethromycin failed to demonstrate an ability to accumulate to clinically useful concentrations during human trials and was not approved by the Federal Drug Administration for use in treatment of mild to moderate community-acquired pneumonia (FDA 2009). Other macrolide candidates discontinued during clinical trials in recent years include modithromycin (EDP-420) and another bridged bicyclic macrolide, EDP-788 (Bermudez et al. 2007; Jacobsson et al. 2015).