



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy



NEW DRUGS VIII

Telithromycin (Ketek®)

Approved indications: Community-acquired pneumonia (mild to moderate) (CAP), acute bacterial exacerbation of chronic bronchitis (AECB), and tonsillitis/pharyngitis (patients intolerant to beta-lactam antibiotics).

Mechanism of action: Telithromycin is a synthetic derivative of erythromycin, with a mechanism of action and spectrum of antibiotic sensitivity and resistance similar to other macrolide antibiotics.

Pharmacokinetics: Telithromycin is 60% bioavailable by mouth and widely distributed throughout the body. The half-life is 10 hours. Inactivation is primarily by liver metabolism, with approximately 50% mediated by CYP 450 (3A4).

Evidence of efficacy: Randomized controlled trials (RCTs) in patients with CAP: clinical cures were similar for telithromycin (70%) and clarithromycin (72%)¹; clinical cures were similar for telithromycin (81%) and amoxicillin (73%).²

RCT in patients with tonsillitis/pharyngitis: clinical cures were similar for telithromycin (77%) and clarithromycin (74%).³

RCTs in AECB: clinical cures were similar for telithromycin (57%) and cefuroxime (56%)⁴; clinical cures were similar for telithromycin (74%) and amoxicillin/clavulate (71%).⁵

Telithromycin has not been compared with erythromycin, azithromycin or spiramycin in CAP, AECB or tonsillitis/pharyngitis.

Adverse effects: Serious adverse events, including deaths, did not differ significantly in any trial. In pooled Phase I studies, the QTc interval increased by 3.9 msec per 1 mg/L increase in serum telithromycin concentrations. In controlled clinical trials interactions with drugs metabolized by CYP 3A4 and 2D6 further lengthened QTc duration.¹

Nausea was more common in patients on telithromycin (8%) than amoxicillin (3%).² Three adverse effects were higher for telithromycin than clarithromycin: diarrhoea (18% vs. 8%), nausea (11% vs. 4%), and vomiting (6% vs. 1%).³ Two adverse effects were higher for telithromycin than cefuroxime: nausea (9% vs. 3%) and gastrointestinal pain (3% vs. 0%).⁴ Adverse effects were higher for amoxicillin/clavulate than telithromycin: total (37% vs. 24%) and diarrhoea (10% vs. 3%).⁵

When the RCTs were pooled, more patients had an episode of blurred vision with telithromycin than



comparators (0.9% vs. 0.2%). These episodes occurred more frequently in women than men, and were mainly non-serious and reversible.

Dose and cost: Approved dose is 800 mg once daily for 10 days for CAP (\$66) and 800 mg once daily for 5 days for AECB and tonsillitis/pharyngitis (\$33). Approximate cost for a course of therapy for CAP: erythromycin, \$5, azithromycin, \$32, clarithromycin, \$32 - \$64.

CONCLUSION: Telithromycin is of similar efficacy to but has more adverse effects than clarithromycin, the one macrolide to which it has been compared.

Ezetimibe (Ezetrol®)

Approved indication: Hypercholesterolemia administered alone or with a statin.

Mechanism of action: Ezetimibe is the first lipid lowering compound that selectively inhibits the intestinal absorption of cholesterol.

Pharmacokinetics: Ezetimibe is rapidly absorbed and metabolized to ezetimibe-glucuronide, an active metabolite. The half-life of both active compounds is approximately 22 hours. Inactivation is primarily by excretion in the bile and there is significant enterohepatic recycling.

Evidence of efficacy: In 6 double blind (DB) placebo controlled trials of 12 weeks duration, ezetimibe, 10 mg/day, lowered LDL cholesterol by a mean of 18%.⁶⁻¹¹ The dose of atorvastatin to achieve a similar reduction in LDL cholesterol is 1.25 mg/day. In 6 DB placebo controlled trials of 8-12 weeks duration ezetimibe, 10 mg/day, plus a statin lowered LDL cholesterol by a mean of 16% compared to placebo plus a statin.⁸⁻¹³

Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: (604) 822-0700
Fax: (604) 822-0701
E-mail: info@ti.ubc.ca
Web: www.ti.ubc.ca
(all Therapeutics Letters, Course Information)

Adverse effects: Serious adverse events were not reported in 7 of the 8 trials. Reported adverse effects, including gastrointestinal symptoms, were not significantly different in patients taking ezetimibe as compared to placebo.

Dose and cost: Approved dose is 10 mg once daily (\$1.70).

CONCLUSION: Ezetimibe alone or when added to a statin lowers LDL cholesterol by 16 to 18% in 3-month trials. It is unknown whether ezetimibe therapy for longer time periods will be beneficial or harmful.

Topical Pimecrolimus (Elidel®) and Tacrolimus (Protopic®)

Approved topical indications: Atopic dermatitis in patients aged two years or older, who are non-responsive to or intolerant of conventional therapies.^{14,15} Pimecrolimus is approved for *mild to moderate* atopic dermatitis¹⁴ whereas tacrolimus is approved for *moderate to severe* atopic dermatitis.¹⁵

Mechanism of action: Both inhibit calcineurin phosphatase and have actions similar to cyclosporine. They reduce cytokine production and T cell activation, as well as other pro-inflammatory processes such as mast cell mediator release. Their precise mechanisms of action in atopic dermatitis are unknown. **Tacrolimus is also used intravenously and orally as an immunosuppressant in organ transplantation patients.**

Pharmacokinetics: Systemic absorption results in some patients having consistently measurable blood levels, while other patients do not, despite similar skin involvement.¹⁶⁻²² Both pimecrolimus and tacrolimus are inactivated by liver metabolism (primarily CYP 3A4).^{15,17}

Evidence of efficacy:

Topical 1% Pimecrolimus Cream:

Children aged 2-17 years: Pimecrolimus has only been compared with a vehicle placebo in children. In two pooled DB RCTs lasting 6 weeks, pimecrolimus was more efficacious than the vehicle placebo.²¹ In a 52 week study, pimecrolimus reduced the incidence of atopic dermatitis flare compared to the vehicle placebo.²²

Adults: Two RCTs compared pimecrolimus with topical corticosteroids: one 3-week study²³ and one larger 52-week study¹⁷. **Both studies demonstrated a therapeutic advantage for topical steroids over pimecrolimus.** The short-term study used a mid-potency corticosteroid, 0.1% betamethasone valerate²³ and excluded head and neck treatment. The longer study used a mid-potency corticosteroid²⁴, triamcinolone acetonide, for trunk and limbs and the lowest potency corticosteroid²⁴, 1% hydrocortisone acetate, for head, neck and intertriginous areas.¹⁷

Topical 0.03% and 0.1% Tacrolimus Ointment:

Children aged 2 – 15 years: In a 3-week RCT tacrolimus 0.03% was superior to the lowest potency corticosteroid, 1% hydrocortisone acetate.²⁵ Fifty-four percent of tacrolimus-treated children who achieved > 90% improvement in a global assessment did not maintain this effect for 2 weeks after discontinuation.

Adults: A 3-week study showed that 0.03% tacrolimus was inferior to 0.1% hydrocortisone butyrate (HCB), a mid-potency corticosteroid.²⁶ 0.1% tacrolimus had similar efficacy to HCB but a greater incidence of application site adverse events. Forty-one percent of those who had responded with a >90% improvement in the 0.1% tacrolimus group did not maintain the improvement 2 weeks later.

Adverse effects:

Most common: application site effects (burning and pruritus).

Common: flu-like syndrome and headache.

Potentially serious: possible increased risk of infection, particularly viral infection.^{14,15,17,18} Follow-up to date has been insufficient to assess long-term adverse effects (local or systemic).

Based on experience with systemic calcineurin inhibitors and pre-clinical data for topical use, possible harms include malignancy (eg. skin cancer and lymphoma).

Pimecrolimus and tacrolimus are not recommended in immunocompromised patients or those with active infection.^{14,15,17,18}

Dose and cost: *Pimecrolimus cream 1%:* applied bid in children and adults (approximate daily cost: \$3 - \$5).

Tacrolimus ointment: children - 0.03% applied bid (approximate daily cost: \$3 - \$4); adults - 0.1% applied bid (approximate daily cost: \$4 - \$6).

CONCLUSIONS:

- Pimecrolimus has not been compared with corticosteroids in children and has a therapeutic disadvantage versus corticosteroids in adults.

- Tacrolimus was more efficacious in children than the lowest potency corticosteroid, 1% hydrocortisone acetate. Tacrolimus has a therapeutic disadvantage versus corticosteroids in adults.

- **Long-term harmful effects associated with systemic absorption of these immunosuppressant drugs, especially in children, are unknown.**

REFERENCES

The references for this Therapeutics Letter are available along with the web version of this Letter on the TI web site: www.ti.ubc.ca/pages/letter51.htm

This Letter contains an assessment and synthesis of publications up to April 2004. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 50 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.