slows the sinoatrial pacemaker (Hale JJ et al., *Bioorg Med Chem Lett.* 2004, 14(13): 3501-5; Bünemann M et al., *J Physiol* 1995, 489: 701-707; Guo J et al., *Pflugers Arch* 1999, 438: 642-648; Ochi R et al., *Cardiovasc Res* 2006, 70: 88-96). Moreover, the non-selective S1P receptor agonist FTY720 reduces heart rate in humans (Koyrakh L et al., *Am J Transplant* 2005, 5: 529-536), and the literature suggests that $S1P_1$ selective compounds would have diminished effects on heart rate in humans, compared to non-selective S1P receptor agonists (Himmel HM et al., *Mol Pharmacol* 2000, 58: 449-454; Peters SL, Alewijnse AE, *Curr Opin Pharmacol.* 2007, 7(2): 186-92; Fujishiro J et al., *Transplantation* 2006, 82(6): 804-12; Sanna MG et al., *J Biol Chem.* 2004, 279(14): 13839-48).

Summary

In one aspect of the invention, there is provided the use of (R)-5-[3-Chloro-4-(2,3-dihydroxy-propoxy)-benz[Z]ylidene]-2-([Z]-propylimino)-3-o-tolyl-thiazolidin-4-one (Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment and/or prevention of diseases or disorders selected from the group consisting of rejection of transplanted organs selected from kidney, liver, heart and lung; graft-versus-host diseases brought about by stem cell transplantation; autoimmune syndromes selected from rheumatoid arthritis, multiple sclerosis, psoriasis, psoriatic arthritis, Crohn's disease, and Hashimoto's thyroiditis; and atopic dermatitis, wherein said medicament is to be administered orally to a subject in such a way that during the initial treatment phase Compound 1 is to be administered at an initial dose that is between 2- to 5-fold lower than the target dose, until no further acute heart rate reduction occurs, wherein acute heart rate reduction refers to a heart rate decrease from pre-dose values of 10 or more beats per minute (bpm) that is maximal within 1-3 hours after drug administration, followed by dose up-titration to the target dose, wherein the target dose is 20 or 40 mg of Compound 1 to be administered p.o. once daily, wherein the dose below the target dose is to be administered at a dosing frequency of once or twice daily and wherein dose up-titration to the target dose is to be done in one or several dose increments.

Description of the invention

The compound (R)-5-[3-chloro-4-(2,3-dihydroxy-propoxy)-benz[Z]ylidene]-2-([Z]-propylimino)-3-o-tolyl-thiazolidin-4-one (hereinafter also referred to as "Compound 1"; the preparation of Compound 1 and the medicinal use thereof, is described in the published PCT application WO 2005/054215) is a selective $S1P_1$ receptor agonist, and repeated daily oral dosing of 5 mg or more to humans results in a consistent, sustained, and dose-dependent reduction in the number of peripheral blood lymphocytes. It has been surprisingly found, however, that the selective $S1P_1$ receptor agonist Compound 1 transiently reduces heart rate in humans, with maximal effects 1-3 hours after administration. In some individuals this is accompanied by similarly transient increases in the PR interval in the electrocardiogram (ECG), and an associated irregular heart rhythm (so-called Wenckebach rhythm). Occasional fatigue or dizziness also occur in the post-dose period. These acute effects of Compound 1 on heart rate and rhythm and fatigue/dizziness are milder at 10 mg than at 20 mg. All of these effects wane with repeated dosing. Thus, after 2 to 4 days of daily oral doses of 5 to 20 mg, an acute heart rate reduction, compared to the pre-dose value, is no longer observed upon administration of Compound 1. Similarly, with repeated daily oral dosing of 5 to 20 mg of Compound 1, transient increases in the PR interval of the ECG relative to pre-dose values are not observed, nor are fatigue or dizziness reported. The acute effects on heart rate, atrioventricular conduction, or fatigue and dizziness, although not seriously adverse, are undesirable, and methods to minimize these effects would be valuable for maximizing the tolerability and safety of Compound 1, and other selective $S1P_1$ receptor agonists, and minimizing associated monitoring requirements, in the early phase of dosing initiation, or, after a drug interruption, at re-initiation of drug therapy.