Summary

Losartan in Marfan syndrome - Dr. R. Franken

Uncertainty surrounds the benefit of preventive pharmacological therapies in reducing aortic disease in patients with Marfan syndrome. Patients with Marfan syndrome are at increased risk of premature death when untreated. To reduce the risk of aortic complications, patients with Marfan syndrome undergo elective aortic surgery when the diameter of the aorta exceeds 50 mm.

The current most frequently prescribed preventive pharmacological treatment is β-blockade to reduce aortic haemodynamic stress. However, for 20 years, β-blockade has been prescribed on the basis of studies with conflicting results, and only one small, prospective, randomized study of 70 patients. Now, the uncertainty of treatment continues with losartan. Losartan might be an alternative or complementary therapy to β-blockers, given that losartan reduces arterial pressure and antagonizes transforming growth factor β, a protein that is found at elevated levels in patients with Marfan syndrome and which is associated with severity of cardiovascular disease.

After evidence for the effectiveness of losartan in a mouse model of Marfan syndrome, losartan significantly decreased the rate of aortic dilatation from 3.54 ± 2.87 mm per year to 0.46 ± 0.62 mm per year (P <0.001) in a retrospective, observational study of 18 children with a rapid rate of aortic dilatation despite other medical therapy. Worldwide, eight randomized clinical trials were initiated to test whether losartan given in addition to, or instead of, β-blockers would be beneficial in reducing the rate of aortic dilatation in patients with Marfan syndrome. So far, six studies have been published (Table 1).

Country	Design	Treatment	FU	Age (years)	Number	Imaging	AoD (mm/yr)	Death and dissection
Taiwan	OL, BE	L + BB vs BB	35	13 ± 6	29 (28)	US	0.10 vs 0.89 (p=0.02)	1 vs 0
Holland	OL, BE	L vs no L	37	38 (>18)	233 (145)	MRI/US	0.26 vs 0.45 (p=0.014)	0 vs 2
USA	DB	L vs BB	36	11(0-25)	608 (535)	US	0.75 vs 0.69 (p=0.20)	3 vs 0
France	DB	L vs placebo	42	30 (>10)	297 (292)	US	0.44 vs 0.51 (p=0.37)	1 vs 5
Spain	DB	L vs BB	36	5-60	150	MRI/US	0.37 vs 0.47 (p=0.326)	1 vs 4
Belgium	DB	L vs placebo	36	>10	22	US	0.33 vs 0.33 (p=1.0)	0 vs 1
UK	DB	I vs placebo	48	6-40	490	US		
Italy	OL, BE	L vs BB vs L+BB	48	1-55	291	US		

Table 1. The eight initiated randomised trials, of which the first six are published.

AoD: aortic root dilation rate, BB: beta-blocker, BE: blinded endpoints, FU: follow-up (in months), I: irbesartan, L: losartan, OL: open label

At first, a small pilot study demonstrated that losartan (50 mg in children, 100 mg in adults) combined with β-blockers (2 mg/kg in children, maximum of 150 mg in adults, n = 15) significantly reduced the rate of aortic root dilatation compared with β-blockers alone (n = 13; 0.10 vs 0.89 mm per year; P = 0.02) measured using echocardiography during 35 months of follow-up. The COMPARE trial demonstrated the beneficial effect of losartan added to baseline therapy (mostly β-blockers [74%], 50–100 mg) compared with no losartan in a study with an open-label design and blinded end points. After 37 months of follow-up, losartan (n = 76) significantly reduced the rate of aortic root dilatation compared with no losartan (n = 61) in patients with a native aortic root (0.26 vs 0.45 mm per year; P = 0.01), and the rate of aortic arch dilatation in patients with previous aortic root surgery (0.17 vs 0.34 mm per year; P = 0.03), as measured using MRI. In line with the results of the Marfan Sartan trial, losartan seemed to be more effective in reducing the rate of aortic dilatation in patients with an *FBN1* mutation. The investigators in the Pediatric Heart network study compared losartan versus atenolol in a large, blinded trial including 608 children (mean age 11 years, range 0.5–25.0 years) with the use of echocardiography during 36 months of follow-up. They demonstrated that losartan (1.3 mg/kg, maximum of 100 mg) and β-blockers (2.7 mg/ kg, maximum of 250 mg) were both effective in reducing the aortic z-score, but losartan was neither superior nor inferior to atenolol (–0.107 vs –0.139 z-score per year; P = 0.08). In the randomized, placebo-controlled Marfan Sartan trial, investigators evaluated the benefit of adding losartan to baseline therapy in 292 patients aged >10 years. During 3.5 years of follow-up, 146 patients received losartan (50 mg if <50 kg [15%] or 100 mg if ≥50 kg [85%]), and 146 patients received a placebo in addition to baseline therapy (86% received β-blockers, mean dosage 65 mg). The rate of aortic root dilatation was measured by linear regression lines using echocardiography performed every 6 months as mean change in z-score per year. Similar aortic dilation rates were found for the losartan and placebo groups (–0.03 vs –0.01 z-score per year; P = 0.69), as was the mean change in dilatation rate (0.44 vs 0.51 mm per year; P = 0.36). Losartan tended to be more beneficial in patients with an *FBN1* mutation compared with those without (–0.04 vs 0.00 z-score per year and 0.40 vs 0.51 mm per year; P value not reported). In Spain a double-blind study was conducted in 140 MFS patients, age range 5–60 years, with maximum aortic diameter <45 mm who received losartan (n = 70) or atenolol (n = 70), maximum of 1.4 mg/kg/day or 100 mg/day. After 3 years of follow-up, aortic root diameter increased similar in both groups (losartan: 1.1 mm vs atenolol 1.4 mm, P = 0.382) and indexed by BSA (losartan −0.5 mm/m2 as compared to atenolol, P = 0.092). The last published trial so far is conducted in Belgium were 22 patients were enrolled showing similar increase in the aortic root during the 3 years of follow-up in both groups (median 1 mm, IQR [-1-1.5] and 1 mm, IQR [-0.25-1], p = 1).

How can we explain the discrepancies between the results of these studies? Important differences exist in study design, which might explain the variability in outcome. Firstly, the use of placebo is preferable to an open-label design. the open-label design of the pilot study and the COMPARE trial might, theoretically, have positively influenced the beneficial effect of losartan. Secondly, losartan in addition to β-blockers was investigated in three studies, whereas losartan was compared with β-blockers in one study. Furthermore, the dosage of the β-blocker used varied from low to very high, both within and between the studies. Thirdly, the use of MRI in the

COMPARE trial is more accurate than echocardiography, especially for measurements of only several millimetres of growth. Aortic root asymmetry and chest deformation are well-known features in Marfan syndrome, indicating that the high interobserver variability with echocardiography might limit its value in a clinical trial over 3.5 years, during which the aorta dilates only 0.1–0.9 mm per year. Fourthly, study population size and differences in power calculation might influence the results of the different studies. investigators in the COMPARE trial did not enroll the intended 330 patients. the results of the Marfan sartan trial were based on intention-to-treat analysis, but 69 patients prematurely stopped the trial drug (28% of those in the losartan group), thereby diluting a possible beneficial effect of losartan. Lastly, the age of the included patients differed substantially between the four studies. A post-hoc sub analysis between children and adults in the Marfan sartan trial might be informative.

The large heterogeneity of Marfan syndrome might be an alternative explanation for the present uncertainty about the effect of losartan on aortic dilatation. the type of *FBN1* mutation might influence the drug response. Indeed, in a small substudy of the COMPARE trial, patients with an *FBN1* mutation leading to haploinsufficiency responded better to losartan treatment than patients with a dominant-negative *FBN1* mutation. As haploinsufficient mutations comprise only around 35% of *FBN1* mutations, the effect of losartan on the overall Marfan population might have been masked by the larger number of dominant-negative mutations. These analyses should be explored in more depth in larger cohorts. The two ongoing trials should be awaited to have a complete overview of losartan and β-blocker treatment in Marfan syndrome. However, a meta-analysis of the first studies revealed that losartan does not seem to be more effective in reducing the rate of aortic dilatation than a high dosage of β-blockers. Losartan in addition to β-blockers seems to be more effective than a low dosage of β-blockers (50–100 mg). Even when added to β-blocker therapy, losartan is well-tolerated and a safe treatment option in patients with Marfan syndrome. Losartan can be administered as an alternative treatment when β-blockers are not well tolerated. Losartan does not seem to be a panacea in the treatment of aortic disease in Marfan syndrome. However, losartan can safely be administered as an alternative treatment to β-blockers or in addition to low-dose β-blockers.

Partly adapted from:

Losartan versus atenolol in the Marfan aorta – How to treat

Nature Review Cardiology 2015;12(8):447-8

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