Medical Treatment in Marfan Syndrome

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Why do we have to treat?

Flo Hyman (1954 -1986)
Captain of the American Women’s Olympic Volleyball team
Died during a match in Japan at age 32
Acute aortic dissection
Post mortem diagnosis of MFS

70 - 100 % of overall mortality in MFS is due to cardiovascular complications

To avoid aortic dissection
Is treatment useful?

 Survival:
- Earlier diagnosis
- Surgical treatment
- Medical treatment

Silverman et al, Am J Cardiol 1995

YES
Current Medical Treatment in MFS

β-blockers

Hemodynamic effect (lower dp/dt)

→ Slow rate of aortic dilatation

Optimal result when

- Started early in life
- Aortic diameter ≤ 40mm

Non-responders

No hard end-points!

Shores et al, NEJM 1994
Current Medical Treatment in MFS

\(\beta\)-blockers - Pro’s and Con’s

“Beta-blockade appears to limit aortic dilatation during childhood in patients affected by Marfan syndrome. Therefore this treatment should be recommended as soon as the diagnosis is made”

*M Ladouceur* Am J Cardiol 2007;99:406-409

“This study suggests that beta-blocker therapy does not significantly alter the rate of aortic root dilatation in children with Marfan syndrome. Based on these data, the recommendation of lifetime beta-blocker therapy instituted during childhood should be reassessed”

*S Tierney* J Pediatr 2007; 150:77-82
Alternatives?

Calcium channel blockers?
Rossi-Foulkes, R., et al., Am J Cardiol, 1999

ACE inhibitors?
Yetman, A.Tet al., Am J Cardiol, 2005

Based on the assumption of similar hemodynamic effects as beta-blockers

Mainly used in patients intolerant for beta-blockers
Alternatives?
Marfan

NAB Losartan

Microfibril/Fibrillin

LAP

Co-Activators, Co-repressors
Transcription Factors
Gene transcription

Nucleus

Tβ-RII

Tβ-RI

Receptor Complex

Sma2 2
Sma3 3
Sma4

Smad2 2
Smad3 3
Smad4

TGFβ

P

P

Losartan
TGFβ-inhibition

TGFβ-inhibition
New treatment opportunities

Losartan in Humans:  
“a small molecule for a large disease”
New treatment opportunities

Results: aortic root growth
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<tr>
<th>Location</th>
<th>Study Drug</th>
<th>Design</th>
<th>Target Number</th>
<th>Inclusion</th>
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The Marfan Trialists’ Collaboration
A prospective, collaborative meta-analysis of individual patient data from all randomised trials of angiotensin receptor antagonists in Marfan syndrome

• >2,400 patients: reliable estimate of effect size
• Large enough to explore variation in effect size
• Maximise power to detect clinical endpoint differences
• Estimates of effect sizes for ARBs…..and Beta-blockers

A. Pitcher – Oxford UK
Alternatives?
Angiotensin pathway

- Enalapril (ACEi)
- Losartan (ARB)
- AngI → AngII
- AT1
- AT2
- ↑ TGFβ ligands
- ↑ TGFβ receptors
- ↑ TGFβ signaling
- ↑ TSP-1
- ↓ Proliferation
- ↓ Apoptosis
- ↓ Fibrosis
- ↑ MMP2, MMP9
- ↓ Proliferation
- ↑ Apoptosis
- ↓ Fibrosis
- ↓ MMP9
Angiotensin pathway

- Losartan uniquely inhibits TGFβ mediated activation of ERK, by allowing continued signaling through AT2
- Enalapril limits signaling through both receptors and is less effective

New Treatment Opportunities

- Both pathways (canonical and non-canonical) are activated in a MFS mouse model
- Both are inhibited by R/ directed against TGFβ (NAB, losartan)
- Selective ERK inhibition ameliorates aortic growth
- Smad 4 deficiency exacerbates aortic disease
- Non-canonical (Smad-independent) TGFβ signaling is a prominent driver of aortic disease
- ERK1/2 or JNK inhibition is a potential therapeutic target
ERK1/2 Antagonist RDEA-119 Arrests Aortic Root Growth in a Mouse Model of MFS

Holm et al, Science 332, 358 (2011)
Doxycyclin
Doxycyclin

• Inhibition of MMP-2 by doxycycline delays the manifestations of MFS, in part, through its ability to decrease active TGF-β and the noncanonical signaling cascade downstream of TGF-β

• Combination therapy with doxycycline and losartan was more effective than either drug alone

➢ targeting TGF-β signaling at different points might be a more effective strategy for inhibiting disease progression.
Conclusions

Treatment of cardiovascular manifestations in patients with Marfan syndrome has a significant effect on life-expectancy

Medical treatment with β-blockers is effective in most patients

Recent insights into the pathophysiology of Marfan syndrome offer promising opportunities for medical treatment via interaction with the TGFβ pathway

Large scale trials with losartan are underway and results need to be awaited before treating larger groups of patients