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Review

Recent Clinical Drug Trials Evidence in Marfan Syndrome and Clinical Implications

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ABSTRACT

Marfan syndrome is a genetic disorder of connective tissue with principal manifestations in the cardiovascular, ocular, and skeletal systems. Cardiovascular disease, mainly progressive aortic root dilation and aortic dissection, is the leading cause of morbidity and mortality. The primary aims of this report were to examine the evidence related to medical therapy for Marfan syndrome, including recently completed randomized clinical trials on the efficacy of β-blockers and angiotensin II receptor blockers for the prophylactic treatment of aortic enlargement in Marfan syndrome, and to provide recommendations for medical therapy on the basis of available evidence. Medical therapy for Marfan syndrome should be individualized according to patient tolerance and risk factors such as age, aortic size, and family history of aortic dissection. The Pediatric Heart Network trial showed that atenolol and losartan each reduced the rate of aortic dilation. All patients

RÉSUMÉ

Le syndrome de Marfan est une maladie génétique caractérisée par une anomalie du tissu conjonctif pour laquelle ses principales manifestations sont observées sur les systèmes cardiovasculaires, oculaire et squelettique. Les maladies cardiovasculaires, principalement la dilatation progressive de la racine aortique et la dissection aortique, sont les principales causes de morbidité et de mortalité. Les principaux objectifs du présent rapport sont d'examiner les données probantes liées au traitement médical du syndrome de Marfan, dont celles des essais cliniques aléatoires récemment achevés sur l'efficacité des β-bloquants et des bloqueurs du récepteur de l'angiotensine II en matière de traitement prophylactique de l'élargissement de l'aorte lors de syndrome de Marfan, et de donner des recommandations de traitement médical en s'appuyant sur les données probantes disponibles. Le traitement médical du syndrome de Marfan devrait être adapté en

Marfan syndrome is a genetic disorder of connective tissue with autosomal dominant inheritance and principal manifestations in the cardiovascular, ocular, and skeletal systems. The syndrome, which affects approximately 1 in 5000 individuals, is caused by mutations in *FBN1*, the gene that encodes fibrillin-1, a component of extracellular microfibrils. Cardiovascular disease, mainly progressive aortic root dilation and aortic dissection, is the leading cause of morbidity and mortality. Advances in clinical and molecular diagnosis, as well as medical and surgical management including serial cardiac imaging, exercise restriction, administration of β-adrenergic receptor antagonists (β-blockers [BBs]), and elective aortic root replacement, are associated with improved survival and quality of life.

Our understanding of the pathogenesis of Marfan syndrome and current options available for medical therapy are evolving. The primary aims of this report were to examine the evidence related to medical therapy for Marfan syndrome, including recently completed randomized clinical trials on the efficacy of BBs and angiotensin II receptor blockers (ARBs) for the prophylactic treatment of aortic enlargement in Marfan syndrome, and to provide recommendations for medical therapy on the basis of available evidence.

Throughout, plus-minus values indicate mean ± SD unless otherwise specified.

β-Blockers

Citing several lines of evidence, Halpern and colleagues[1] suggested in 1971 that β-adrenergic blockade might reduce the risk of aortic dissection, by reducing the rate of change in central aortic pressure with respect to time (designated as dP/dt) or the impulse of left ventricular ejection. In an open-label, randomized trial conducted to compare propranolol with no therapy in 70 teenagers and adults with Marfan syndrome, Shores and colleagues[2] showed a significantly reduced rate of aortic enlargement among treated patients (Table 1). The dose of propranolol was individualized (mean dose ± standard error [SE], 212 ± 68 mg/d), uptitrated to achieve a specific hemodynamic effect, with a goal of decreasing exercise heart rate and left ventricular contractility (increasing the systolic time interval measured using echocardiography, corrected for

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with known or suspected Marfan syndrome and aortic root dilation should receive medical therapy with adequate doses of either β-blocker or angiotensin receptor blocker. The Pediatric Heart Network trial also showed that atenolol and losartan are more effective at reduction of aortic root *z* score in younger subjects, which suggests that medical therapy should be prescribed even in the youngest children with aortic dilation. For patients with Marfan syndrome without aortic dilation, the available evidence is less clear. If aortic dilation is severe and/or progressive, therapy with a combination of β-blocker and angiotensin receptor blocker should be considered, although trial results are mixed with respect to the efficacy of combination therapy vs monotherapy.

fonction de la tolérance et des facteurs de risque du patient comme l'âge, la taille de l'aorte et les antécédents familiaux de dissection aortique. L'essai du Pediatric Heart Network montrait que l'aténolol et le losartan réduisaient tous deux le taux de dilatation de l'aorte. Tous les patients chez qui l'on connaît ou soupçonne le syndrome de Marfan et la dilatation de la racine aortique devraient recevoir le traitement médical à des doses suffisantes de β-bloquants ou de bloqueurs du récepteur de l'angiotensine. L'essai du Pediatric Heart Network montrait également que l'aténolol et le losartan sont plus efficaces pour réduire le Z-score de la racine aortique chez les plus jeunes sujets, ce qui suggère que le traitement médical devrait être prescrit même chez les plus jeunes enfants ayant une dilatation de l'aorte. Quant aux patients atteints du syndrome de Marfan qui n'ont pas de dilatation aortique, les données probantes disponibles sont moins évidentes. Si la dilatation de l'aorte est grave et/ou progressive, le traitement qui combine les β-bloquants et les bloqueurs du récepteur de l'angiotensine devrait être considéré, bien que les résultats de l'essai sur l'efficacité du traitement combiné *vs* la monothérapie soient mitigés.

the heart rate, by 30%). Freedom from clinical end points (death, congestive heart failure, aortic regurgitation, aortic dissection, cardiovascular surgery) was higher in the treated group, although the difference was not statistically significant beyond 9 years. Subsequent studies of the efficacy of BBs in Marfan syndrome (Table 1) have shown mixed results; some showed benefit and some did not[3-9]; however, none of the other studies titrated the BB dose to hemodynamic effect. Despite debate about their efficacy in individuals with Marfan syndrome, BBs have become the mainstay of medical management. However, many patients experience progressive aortic dilation despite BB therapy, with ongoing risk for aortic dissection and need for prophylactic aortic root surgery.

Angiotensin Receptor Blockers

Our understanding of the role of fibrillin-1 (FBN1) in the pathogenesis of Marfan syndrome is evolving. FBN1 was traditionally viewed as a structural protein that contributed to the structural integrity of connective tissue. However, we now understand that normal fibrillin-1 plays a regulatory role by binding the latent complex of the cytokine transforming growth factor β (TGFβ), regulating its activation and signalling. Studies in an FBN1-deficient mouse model of Marfan syndrome have shown that deficiency of FBN1 is associated with abnormal signalling of TGFβ. Excessive TGFβ activation and signalling are now thought to contribute to the multisystem clinical manifestations of Marfan syndrome, including aortic root dilation and dissection.[10,11]

Losartan, an angiotensin II type 1 receptor blocker, has been shown to attenuate TGFβ signalling in some disease states, such as chronic renal failure. Marfan mice treated with losartan showed a rate of aortic root growth similar to that in wild type mice and significantly less than that of untreated littermates with Marfan syndrome. The BB propranolol also slowed the rate of aortic root growth in Marfan mice, but this effect was much less pronounced than that seen with losartan. Losartan therapy in mice with Marfan syndrome prevented elastic fibre fragmentation and preserved aortic wall architecture.[12] Losartan therapy showed a striking decrease in the rate of aortic root growth in a small series of severely affected children with Marfan syndrome in whom conventional therapy had failed (Table 2).[13] Losartan also decreased the rate of aortic root growth in 2 small series of more typically affected children with Marfan syndrome, but to a lesser degree.[14,15]

Randomized Trials

On the basis of these early studies, 10 randomized controlled trials of ARBs in patients with Marfan syndrome were initiated, each designed to evaluate the effect of ARBs, compared with either β-blockade or placebo/open-label control, on aortic root size and growth rate, as well as other aspects of cardiovascular and noncardiovascular structure and function (Tables 3 and 4).[16-31] These studies were designed to answer a number of important questions regarding efficacy, safety, and tolerability of ARB and BB therapy.

Trials That Compared ARB Combined With Baseline Therapy vs No Additional Therapy

Several trials were designed to compare an ARB combined with baseline therapy vs no additional therapy, either open-label with a control group, or with a double-blind, placebo-controlled design (Table 3). Irbesartan was the ARB in the United Kingdom trial, and losartan was the ARB in all other trials. The Italian trial design was a 3-way, 1:1:1 randomization to losartan alone, nebivolol alone, and losartan with nebivolol. The trialists in Taiwan, The Netherlands, and France have published their main results, whereas the trial results from Italy, Belgium, and the United Kingdom have not yet been published. We review herein the published evidence to date.

Taiwan

Chiu and colleagues[28] published a randomized, open-label, single-centre pilot study designed to assess the efficacy of losartan combined with β-blockade therapy, vs β-blockade therapy alone, in 28 patients with Marfan syndrome on the