Archives of Cardiovascular Disease (2010) 103, 317—325

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

CLINICAL RESEARCH

Rationale and design of a randomized clinical trial (Marfan Sartan) of angiotensin II receptor blocker therapy versus placebo in individuals with Marfan syndrome

Étude randomisée «MarfanSartan» comparant un antagoniste de l'angiotensine II au placebo chez des patients présentant un syndrome de Marfan

Delphine Detaint[a], Philippe Aegerter[b], Florence Tubach[c], Isabelle Hoffman[c], Henri Plauchu[d], Yves Dulac[e], Laurence Olivier Faivre[f], Marie-Ange Delrue[g], Patrick Collignon[h], Sylvie Odent[i], Maria Tchitchinadze[a], Catherine Bouffard[a], Florence Arnoult[a,j], Mathieu Gautier[a], Catherine Boileau[a,k], Guillaume Jondeau[a,*,l]

[a] *Service de cardiologie, centre de référence pour le syndrome de Marfan et apparentés, hôpital Bichat, 75018 Paris, France*
[b] *Unité de recherche clinique, hôpital Ambroise-Paré, AP—HP, université de Versailles St-Quentin-en-Yvelines, Paris, France*
[c] *Inserm CIE 801, unité de recherche clinique, hôpital Bichat, AP-HP, université Paris-7, Paris, France*
[d] *Service de génétique, hôpital Hôtel-Dieu, université Claude-Bernard, Lyon, France*
[e] *Pédiatrie—Cardiologie, pôle Enfants, hôpital des Enfants, Toulouse, France*
[f] *Centre de génétique, hôpital d'Enfants, université de Dijon, Dijon, France*
[g] *Service de génétique médicale, hôpital Pellegrin Enfants, Bordeaux, France*
[h] *Département de génétique médicale, hôpital d'Enfants de la Timone, Marseille, France*
[i] *Unité de génétique médicale, hôpital Sud, CHU, Rennes, France*
[j] *Service d'explorations fonctionnelles, hôpital Bichat, Paris, France*
[k] *Laboratoire central de biochimie d'hormonologie et de génétique moléculaire, hôpital Ambroise-Paré, AP-HP, Paris, France*
[l] *Inserm, U 698, université Paris-7 Denis-Diderot, Paris, France*

Received 25 February 2010; received in revised form 23 April 2010; accepted 30 April 2010

* Corresponding author. Fax: +33 1 40 25 67 32.
E-mail address: guillaume.jondeau@bch.aphp.fr (G. Jondeau).

1875-2136/$ — see front matter
doi:10.1016/j.acvd.2010.04.008

KEYWORDS
Aorta;
Aortic aneurysm;
Thoracic;
Angiotensin II receptor blocker;
Transforming growth factor beta

Summary
Background. — Recent studies have demonstrated that blockade of the angiotensin II type 1 receptor with losartan decreases aortic damage in an animal model of Marfan syndrome (a KI mouse model with a pathogenic mutation in the gene coding for fibrillin-1).
Aims. — To demonstrate a beneficial effect of losartan on aortic dilatation when added to optimal therapy in patients with Marfan syndrome.
Methods. — This is a multicentre, randomized, placebo-controlled, double-blind, clinical trial with a 2-year inclusion period and a 3-year follow-up period. Aortic root diameter will be measured using two-dimensional echocardiography. Secondary endpoints will include incidence of aortic dissection, aortic root surgery, death, quality of life, tolerance and compliance with treatments. We aim to enrol a total of 300 patients aged $\geq$ 10 years who fulfil the Ghent criteria for Marfan syndrome. Analyses will be based on intention to treat.
Conclusion. — The results of this clinical trial could lead to profound modification of the management of aortic risk and complications in patients with Marfan syndrome and possibly in patients with thoracic aortic aneurysms of other aetiologies.

MOTS CLÉS
Syndrome de Marfan ;
Aorte ;
Anévrisme de l'aorte thoracique ;
Antagoniste des récepteurs de l'angiotensine II ;
TGF-beta

Résumé
Contexte. — Le losartan limite la dilatation aortique sur un modèle de souris KI, porteuse d'une mutation pathogénique du gène *FBN1*, codant pour la fibrilline de type 1.
But de l'étude. — Montrer le bénéfice du losartan ajouté au traitement optimal chez des patients présentant un syndrome de Marfan.
Méthodes. — Étude randomisée, contre placebo, en double insu, avec une période d'inclusion de deux ans et de trois ans de suivi. Le diamètre aortique est mesuré par échographie bidimensionnelle. Les critères secondaires sont l'incidence des décès, de la dissection aortique, de la chirurgie aortique, la qualité de vie, la tolérance et la compliance au traitement. Trois cent patients devraient être inclus (patients de plus de dix ans remplissant les critères de Ghent). L'analyse sera effectuée en intention de traiter.
Conclusion. — Les résultats de cette étude pourraient conduire à modifier la prise en charge de la pathologie aortique et ses complications chez les patients présentant un syndrome de Marfan mais aussi possiblement dans la prise en charge des anévrismes aortiques thoraciques d'autres étiologies.

Background

Marfan syndrome: definition

Marfan syndrome (MFS) is an autosomal dominant disorder with pleiotropic features, including skeletal abnormalities, ectopia lentis and aortic root dilatation. The main causal gene for MFS is FBN1, encoding fibrillin-1, a large glycoprotein that is a main component of extracellular microfibrils. Prognosis is determined mainly by aortic complications (dissection or death), after progressive dilatation of the aortic root. Diagnosis criteria have changed over time; international criteria were proposed in 1988 and refined in 1996, to increase specificity and to integrate genetic testing [1,2]. The current nosology is based on the Ghent criteria, which define major and minor manifestations in different systems (Table [not provided]) [2]. In this setting, the diagnosis of MFS requires at least two major criteria and the involvement of at least one other body system (i.e., three criteria in total). In the presence of an FBN1 mutation or when MFS is diagnosed in a first-degree relative, only one major criterion and the involvement of another body system is required [2]. These Ghent criteria have excellent specificity for FBN1 mutation recognition, because its detection is possible in 95% of patients who fulfil these criteria [3]. However, a mutation in the FBN1 gene is not pathognomonic of MFS and may generate a large array of phenotypes that overlap with MFS (familial ectopia lentis, Shprintzen-Goldberg syndrome, other fibrillinopathies) [4]. On the other hand, some features of MFS can also be present in patients with mutations in the gene coding for transforming growth factor beta (TGFβ) receptor 2 (TGFBR2), who present with MFS type 2 [5—7]. Lastly, mutations in the gene coding for TGFβ receptor 1 (TGFBR1) may also lead to overlapping syndromes [3]. Therefore, defining clear frontiers for MFS, fulfilling the Ghent criteria and differentiating from other clinical conditions that overlap with MFS (MFS type 2, Loeys-Dietz syndrome, familial thoracic aortic aneurysm, Ehlers-Danlos vascular syndrome [8—10]) can sometimes be challenging. In the near future, a revised nosology will emerge, which will focus on the features and criteria that distinguish MFS from other disorders; in the meantime, however, the Ghent criteria remain the reference and will be used for classification of patients in the current study.