"I made myself all things to all men" (1 Cor. 9:22)
" 我為一切人成為一切" (格前 9:22)

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聖保祿醫院
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NEWSLETTER 院訊

Medical Information
醫療資訊

Angiotensin inhibition in diabetic nephropathy

Introduction

Diabetic nephropathy (DMN) is the leading cause of renal failure. It is characterized in its early stage by microalbuminuria, with subsequent development of proteinuria, progressive deterioration of renal function and end stage renal failure (ESRF). Apart from optimal glycemic control, treatment for hypertension and dietary restriction, medical treatment for proteinuria reduction and preservation of renal function are important to delay progression of renal failure.

As with other non diabetic kidney diseases, the initial injury resulting in nephron loss sets in a maladaptive response with compensatory hyperfiltration of the remaining nephrons. This is caused by preferential constriction of the efferent compared to the afferent arterioles, a process mediated by angiotensin II. While this results in increase in intraglomerular pressure with increased filtration of the remaining nephrons, the same process leads to intraglomerular hypertension that will cause further nephron damage in the long run. Renal blood flow to individual nephron is also reduced as a result of afferent arteriolar constriction.

In this context, blockade of renin angiotensin system can help preventing hyperfiltration injury by inhibiting the action of angiotensin II on renal arterioles. The various medications, namely angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) and the newly introduced renin inhibitor, act at different levels of the renin angiotensin system [Figure]. Evidence for their use in DMN are reviewed below.

ACEI or ARB

Both ACEI and ARB are useful in the management of DMN. ACEI is the prototype drug for angiotensin inhibition with a longer experience for its clinical application. In the Captopril diabetes study, captopril has been shown to delay progression of renal failure in type I DM patients with nephropathy independent of blood pressure lowering action [1]. Long term follow up of the same study also showed that sustained remission of proteinuria among patients with nephrotic range proteinuria is achievable with captopril treatment in some patients with preserved renal function [2], suggesting that the renoprotective action of captopril is due to its effect on proteinuria reduction, and persistent proteinuria is associated with worsening renal function in the long run. Among type II DM patients with nephropathy, a fixed dose combination of perindopril and indapamide has been shown to be beneficial with significant reduction of new onset or worsening of microalbuminuria or proteinuria [3]. In this regard, treatment with ACEI is important in early DMN. Furthermore, it may have a role in primary prevention of DMN especially in patients with concomitant hypertension.

The major drawback for ACEI is that it may lead to dry cough in some patients. ARB may be preferred in such cases since it is not associated with dry cough due to absence of bradykinin activation. Apart from a better side effect profile, ARB has also been shown to have renoprotective action in DMN. Two major clinical trials have demonstrated that irbesartan and losartan significantly reduce the risk of doubling of serum creatinine and development of ESRF in type II DM patients with nephropathy [4-5]. These results can generally be applicable to type I DM patients as well. ARB has also been directly compared with ACEI showing that both drugs are comparable with regard to proteinuria reduction and renoprotection in DMN [6].

Combined ACEI and ARB treatment

It is a common clinical scenario that proteinuria may fail to be adequately suppressed despite maximal dosage of ACEI or ARB alone. Combined ARB and ACEI

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treatment may offer additional angiotensin inhibition, which may in turn lead to further proteinuria reduction and better renoprotective effect. The efficacy of combination therapy has been documented in terms of better proteinuria reduction and improved blood pressure control [7-9].

However, the role of combination therapy in long term renoprotection has been questioned by the ONTARGET trial, which compared vascular and renal outcomes in patients with vascular disease or high risk diabetes. It showed that the risk of a composite endpoint of dialysis, doubling of serum creatinine and death was more common in patients on telmisartan plus ramipril therapy compared with either treatment alone despite more significant proteinuria suppression in the combination group [10]. Combination treatment needs to be closely monitored and more studies are needed to clarify its effect in particular on long term renal outcomes.

Renin inhibitor

Aliskiren is the only renin inhibitor introduced recently. As with ARB, it is free of dry cough side effects. In the AVOID trial, combination treatment of aliskiren and losartan in patients with DMN is well tolerated and more effective in proteinuria suppression compared with treatment with losartan alone [11]. However, the follow up duration in this trail lasted six months only. Obviously more data with long term follow up are required to assess the effect of aliskiren or its combination treatment on renoprotection in patients with DMN.

Conclusion

The efficacy of ACEI or ARB is applicable in both type I and II DM patients with nephropathy. Treatment should be started early in the course of DMN. An initial acute rise in serum creatinine may be seen shortly after starting treatment, increase in dosage, adding on combination treatment or if treatment is started relatively late with a high baseline serum creatinine level. This is due to reduction of intraglomerular pressure with angiotensin inhibition resulting in a transient fall in the glomerular filtration rate, which tends to stabilize within the first few months of treatment. A threshold elevation of serum creatinine of up to 35% above baseline level during initial treatment should be acceptable provided close monitoring is done. Patients should also be instructed to have diet restriction to avoid hyperkalemia.

Concerning the choice of agent, ARB may be preferred in view of a better side effect profile with improved patient compliance. Combination treatment with aliskiren (or ACEI) should be considered if proteinuria fails to be adequately suppressed despite maximal dosage of ARB. The general goals of treatment should be blood pressure of less than 130/80mmHg and urine protein excretion of less than 0.5-1g/day or at least >50% reduction from the baseline value. It is hoped that with a multi-modality approach, patients with DMN may benefit with a slowing of progression of chronic kidney disease.

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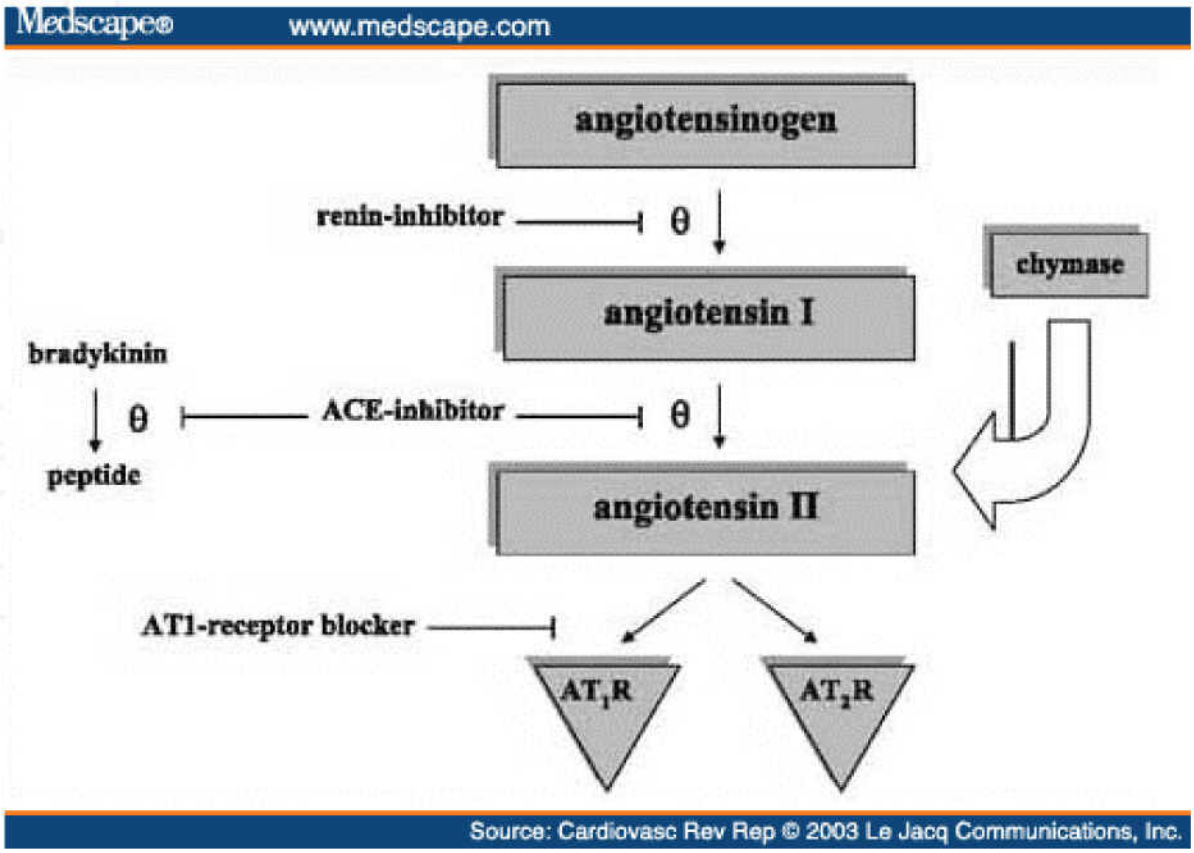
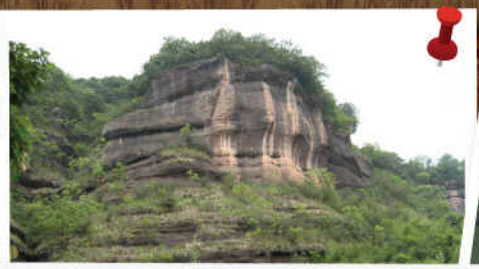
Figure. Mechanism of actions of various medications for angiotensin inhibition (Adapted from www.medscape.com)





二零一零年八、九月份
聖保祿醫院夏季旅行

一年一度醫院夏季旅行 - 韶關丹霞山美食逍遙兩天遊已於八月及九月順利舉行並在乳源麗宮溫泉酒店住宿。參加同事踴躍，總共超過二百多人出席。在日常繁忙的工作中我們難得有機會在醫院以外的地方一同遊玩，渡過一個愉快的假期！旅遊的地方湖光山色，讓我們一同欣賞同事們的精采相片。

As per editorial arrangement, the September's Newsletter was combined its publishment with October's Newsletter.