Seminars in Arthritis and Rheumatism ▮ (2013) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Do current arterial hypertension treatment guidelines apply to systemic lupus erythematosus patients? A critical appraisal

Konstantinos Tselios, MD, PhD[a], Charalampos Koumaras, MD[a], Murray B. Urowitz, MD, FRCPC[b,*], Dafna D. Gladman, MD, FRCPC[b]

[a] Second Department of Internal Medicine, 424 General Military Hospital of Thessaloniki, Thessaloniki, Greece
[b] Centre for Prognosis Studies in Rheumatic Diseases, Toronto Western Hospital, University Health Network, 399 Bathurst St, Toronto, Ontario, Canada M5T 2S8

ARTICLE INFO

Keywords:
Systemic lupus erythematosus
Arterial hypertension
Guidelines
Cardiovascular risk

ABSTRACT

Objective: Arterial hypertension (HTN) is reported to burden up to 74% of systemic lupus erythematosus (SLE) patients and contributes significantly to accelerated atherosclerosis and increased cardiovascular (CV) risk. Current HTN treatment guidelines have not incorporated lupus patients in their recommendations; whether these guidelines can be fully implemented in SLE is doubtful.
Methods: A critical appraisal of the existing HTN guidelines in regard to SLE is presented in this review, based upon clinical and experimental data. Particular issues addressed are the time of antihypertensive therapy initiation, the optimal blood pressure level, the antihypertensive agent of first-choice and the need for reduction of the total cardiovascular risk in SLE.
Results: Antihypertensive therapy should be recommended at levels of 140/90 mmHg (systolic and diastolic BP, respectively) in newly diagnosed lupus patients without overt target organ involvement. In the case of lupus nephritis (LN) or diabetes mellitus (DM), therapy should be implemented at lower levels, such as 130/80 mmHg. Hypertensive lupus patients should be considered at high or very high CV risk and, consequently, the optimal BP level should be less than 130/80 mmHg. Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) seem to be a safe and efficacious first-choice antihypertensive treatment in lupus patients. Total CV risk should be considered and co-morbidities (dyslipidemia, antiphospholipid syndrome, etc.) should be managed promptly.
Conclusions: Current HTN therapeutic guidelines, lacking data from large-scale clinical trials, may not adequately apply to SLE patients. The assessment of the aforementioned recommendations in randomized clinical trials is expected to confirm their value in reducing CV risk in SLE.

Introduction

The use of existing and novel therapeutic modalities in systemic lupus erythematosus (SLE) patients resulted in satisfactory control of disease activity in most cases [1,2]. However, cardiovascular disease (CVD), primarily coronary artery disease (CAD) and cerebrovascular disease, remains a principal cause of death in these patients [3]. It is now widely accepted that lupus patients are at higher (even 50-fold) CVD risk considerably earlier than the general population, which is mainly attributed to the premature atherosclerosis that is associated with SLE [4–7]. Accelerated atherosclerosis represents the cumulative effect of traditional (arterial hypertension, HTN, diabetes mellitus, dyslipidemia, smoking, positive family history, obesity, etc.), lupus-related (inflammatory and autoimmune), and possibly other risk factors on the arterial wall [5,8]. The exact contribution of each of the aforementioned factors to CVD morbidity and mortality in lupus patients has not been thoroughly assessed in prospective, randomized trials. Nevertheless, several studies showed that traditional risk factors account for almost half of the CVD burden in SLE [9–11].

In this context, current guidelines for the management of lupus patients recommend the vigorous control of modifiable risk factors, such as HTN [12]. However, details on the management of this co-morbidity are not specified, thus relying on existing recommendations for the general population [13–16]. Whether these guidelines are entirely applicable to lupus patients is the main issue of this review.

Is HTN really a problem in SLE?

The World Health Organization (WHO) reported HTN and its effects on target-organs (heart, kidneys, brain, etc.) to be the first cause of death worldwide [17]. Therefore, HTN evaluation and management should be the primary goal in any patient. The prevalence of HTN in SLE is reported to vary greatly, reaching 74% in certain cohorts [18–21]. Of note, the prevalence of HTN in non-SLE women is significantly lower, reported to reach 7.7%

* Corresponding author.
E-mail address: m.urowitz@utoronto.ca (M.B. Urowitz).

0049-0172/$ - see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.semarthrit.2013.07.007

between 20 and 44 years of age [22]. Even though the increased prevalence of HTN in SLE remains to be further clarified, systemic inflammation, nephritis, glucocorticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) or their combination may considerably increase baseline blood pressure (BP) in addition to often impeding adequate pharmaceutical treatment of hypertension.

HTN in SLE: Insights into pathophysiology

Lupus nephritis (LN) along with certain immunological abnormalities, such as anti-dsDNA antibodies and low levels of the complement fragments C3 and C4, occurs in nearly 50% of lupus patients and implies a strong correlation with HTN [23,24]. Although HTN may develop independently of LN [25], and not all histological forms of LN carry an increased risk for HTN, it can be speculated that even mild forms of nephritis might have a significant impact on renal hemodynamics and tubular function. In this regard, it was shown that hyperplastic forms of LN (class IV and V) are more commonly related to HTN [26]. It was shown that renal plasma flow and glomerular filtration rate (GFR) are both reduced in LN patients, as a consequence of renal vasoconstriction [27,28]. The ensuing impaired blood pressure–natriuresis relationship results in an increase in BP levels required to excrete excess sodium. In addition, alterations in renal tubular function may also affect HTN pathogenesis and should be evaluated in terms of LN prognosis [29].

Furthermore, alterations of the renal vascular endothelial cell function are believed to play a central role in lupus-related HTN [30]. These alterations probably reflect the generalized endothelial dysfunction in SLE, as circulating autoantibodies and soluble inflammatory mediators are able to activate endothelial cells to upregulate cell adhesion molecules [31]. Additionally, increased levels of circulating endothelial cells and endothelial cell progenitors have been reported in SLE and reflect vascular injury [32,33]. The enhanced apoptosis of endothelial cells is partially mediated by corticosteroids, which are used in the majority of lupus patients [34]. Although the aforementioned endothelial dysfunction may contribute to HTN development in SLE, the underlying pathophysiologic mechanisms are still undetermined.

The activated renin–angiotensin system (RAS) and other endocrine systems are also involved in HTN pathogenesis. Previous studies demonstrated that RAS is activated in lupus patients [35]. Although this is not universal in SLE, early reports suggested that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are most effective in controlling lupus-related HTN [36,37]. In addition to the hemodynamic effects, RAS was shown to promote immune and inflammatory tissue injury, usually mediated by the AT_1 receptor [35]. Although no randomized clinical studies have been performed thus far, experimental data on lupus-prone mice suggest that pharmaceutical RAS inhibition reduces glomerular injury and proteinuria, along with transforming growth factor beta (TGFβ), a major mediator of renal fibrosis [38,39]. Thus, RAS inhibition could have a more profound impact on the immune system in SLE, providing a rational for use in such patients.

An additional mechanism that contributes to HTN progression in SLE is the increased endothelin-1 (ET-1), which promotes renal vasoconstriction and water and sodium retention via ET type A receptor activation [40]. RAS and ET-1 are able to promote the generation of reactive oxygen species (ROS) and increase oxidative stress, which represents an important factor in the pathogenesis of both SLE and HTN [41,42].

Other factors that contribute to HTN progression in SLE are the following: the adipokine leptin, reportedly increased in lupus patients and promoting renal sodium reabsorption, estrogens, and several inflammatory cytokines [43,44]. In particular, IL-6, TNFα, and recently, IL-17 were shown to be related to HTN progression in SLE. IL-6 levels are elevated in SLE and correlate with disease activity [45,46]. Further experimental data suggest that anti-IL-6 antibodies suppress autoimmune responses in lupus-prone mice [47]. IL-6 also promotes Th17 differentiation. Sustained Th17 response may lead to HTN in experimental models of chronic inflammation [48]. The relevant cytokine IL-17 is also elevated in SLE and reflects disease activity [45,46,49]. In contrast, T regulatory cells were found to be quantitatively and/or qualitatively impaired in SLE and HTN [50,51], while the adoptive transfer of these cells in hypertensive mice resulted in marked reduction of the HTN-induced left ventricular hypertrophy and cardiac fibrosis [52,53]. In addition, these inflammatory factors were shown to directly affect angiotensin II, a key molecule in the pathogenesis of HTN [51].

Besides LN and systemic inflammation, the burden of HTN in lupus patients may further deteriorate by the use of certain pharmaceutical agents. Corticosteroids and NSAIDs occasionally contribute to resistant forms of HTN and the development of hypertensive emergencies [54]. Glucocorticosteroids are administered to more than two-thirds of lupus patients [55,56], while NSAIDs are administered to nearly half of them, besides their over-the-counter use [55]. In addition, cyclosporine may be linked to HTN progression, although it is infrequently used in lupus patients [57].

Current concepts in HTN management in SLE

When to initiate drug therapy?

Despite the existence of several HTN therapeutic guidelines, mainly from North American and European authorities [13–16], this issue has not been addressed in SLE; therefore, it is doubtful whether current recommendations can be fully implemented in these patients. In this context, hypertensive lupus patients with early disease and no overt renal and/or cardiovascular involvement are considered either within the general hypertensive population [13,15] or without compelling indication for any specific antihypertensive agent [14].

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) suggests that drug therapy initiation should be considered in any patient whose systolic BP is greater than 140 mmHg and/or diastolic BP greater than 90 mmHg, provided that lifestyle modifications (i.e., smoking cessation, healthy diet focusing on dietary sodium restriction, reduced alcohol intake, increased physical activity, and attaining and maintaining ideal body weight) fail to control BP [13,58]. In addition, patients' stratification is based upon the presence of additional risk factors (i.e., dyslipidemia, diabetes, microalbuminuria or estimated GFR < 60 ml/min, age > 55 years for men and > 65 years for women, and family history of premature CVD) (0, 1–2, and > 3) or according to the estimated total cardiovascular (CV) risk factors. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7 report) further suggests that in patients older than 50 years, systolic BP > 140 mmHg is a more important CV risk factor than diastolic BP; prehypertensive individuals (systolic BP $=$ 120–139 mmHg or diastolic BP $=$ 80–89 mmHg) require health-promoting lifestyle modifications to prevent the progressive rise in blood pressure and CVD [16]. Likewise, the Canadian Hypertension Education Program (CHEP) and the British National Institute for Clinical Excellence (NICE) suggest that drug initiation should be discussed and individualized in patients with Stage 1 hypertension (i.e., clinical blood pressure monitoring (CBPM) of systolic