Discussion

CD4+CD25+ nTregs represent a population of T cells that are highly specialized for suppression of immune responses and are known to play a critical role in the maintenance of peripheral self-tolerance. Approximately one-half of the circulating human peripheral blood lymphocytes express CD4, and of these roughly 10% express the IL-2 growth factor receptor α-chain, CD25, and only those which express high levels of CD25 exhibit suppressive activity in vitro,[16] but, why nTregs cannot eradicate the massive autoimmune response in vivo?

In the present work, circulating CD4+CD25+ regulatory T cells appear in lower numbers in patients with chronic rheumatic carditis than normal persons suggesting an important role for these regulatory T cells in controlling a post-infectious autoimmune disease. Our results (Table 1) show that HR^{WCM} had displayed low prevalence of nTreg cells (1.45%) than SA^{WCM}, negative history and groups of medical care, whereas, patients of SA^{UCM} group had recorded high CD4+CD25+ nTreg cell numbers (4.12%) when compared with HR^{UCM} and patients without continuous medication. Continuous inflammatory state during acute and chronic rheumatic carditis in addition to recurrent attacks of acute rheumatic fever due to exposure to a group A *Streptococcus pyogenes* antigens may lead to reduce frequency of the CD4+CD25+ nTreg cells in the peripheral blood of patients which may occur as a result of an active recruitment of regulatory T cells from circulation to the site of inflammation as a strategy of the immune system to fight an ongoing inflammation. This is consistent with the findings in animal models of chronic inflammatory colitis [17]. A previous study showed that patients with chromosome 22q11.2 deletion syndrome with developmental thymic hypoplasia had markedly fewer CD4+ CD25+ nTreg cells in infancy. That study suggested that patients with chromosome 22q11.2 deletion syndrome had a relatively pure quantitative defect in T-cell production and inclusively CD4+CD25+ nTreg cells which found in fewer numbers in infants, in addition to that, the study suggested that regulation of nTreg-cell production early in life, in humans, is directly related to thymic capacity, and this phenomenon could play a role in the predisposition to autoimmune disease in patients with chromosome 22q11.2 deletion syndrome [18] which may be related with the lower numbers of nTregs in the present CRHD patients if this syndrome is considered one of the causes of autoimmunity in our study.

Nevertheless, we found some of patients had nTregs numbers near to the normal values as in patients with continuous medication, patients number 1, 2, and 3-SA^{UCM} who had 4.17, 4.34, and 4.62 % , and patients number 1, and 4-HR^{UCM} who had 4.62, and 4.44% respectively, and also patient number 7-negative history who had 4.61% of nTregs.

Therefore, many factors may interfere with nTregs function to make them inactive and abrogate their suppressive function. One of these factors believed to play an important role in inhibiting the functional activity of nTreg cells is the tumor necrosis factor alpha. Also, toll-like receptors (TLRs) are primary sensors of both innate and adaptive immune systems and play a pivotal role in the response against structurally conserved components of pathogens. Many researchers found that toll-like receptor-2 signaling in T cells had distinct effects on effectors and nTreg cells. In addition to that, they showed that bacterial lipoprotein (BLP), together with anti-CD3 antibody [T cell receptor (TCR) activation], induced proliferation of both CD4+CD25+ nTregs and CD4+CD25-