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Review Article

The Epidemiology and Treatment of Ankylosing Spondylitis in Korea

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Ankylosing spondylitis is a chronic inflammatory disorder characterized by inflammation of the axial skeleton and sacroiliac joints and to a lesser extent by peripheral arthritis and the involvement of some extra-articular organs. It is paramount for the provision of effective health care delivery to be familiar with the epidemiologic studies on prevalence, mortality, and disability. Furthermore, there is no systematic arrangement of studies related to the treatment of ankylosing spondylitis in Korea. In this review, we addressed Korean ankylosing spondylitis epidemiological studies related to prevalence, genetic factor especially human leucocyte antigen-B27, extra-articular manifestations, infections, mortality, radiologic progression, child-birth, and quality of life. Furthermore, we reviewed Korean ankylosing spondylitis treatment researches about treatment trend, patients' registration program called The KOrean College of Rheumatology BIOlogics and targeted therapy (KOBIO) registry project, biologics and biosimiliars, complications especially infections, and issues about bony progression. There would be value to further studying the epidemiology and treatment of Korean ankylosing spondylitis.

Keywords: Ankylosing spondylitis, Epidemiology, Treatment, Korea

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disorder characterized by inflammation of the axial skeleton and sacroiliac joints and to a lesser extent by peripheral arthritis and the involvement of some extra-articular organs [1]. Although the prognosis of patients with AS varies, the prognosis is determined to some extent by the number of extra-articular manifestations such as uveitis, psoriasis, and inflammatory bowel disease [2,3]. In general, AS causes serious impairment of spinal mobility and function, which greatly reduces the quality of life.

AS sometimes occurs in teenagers, mainly in the 30s, and in rare cases after the age of 45. AS has a worldwide prevalence of 0.1 to 1.4% [4] and is thought to occur more frequently in those with a low socioeconomic status and to result more often in poor functional statuses in this population by affecting the spine [5,6].

The goal of AS treatment is to maintain a stable remission without pain or inflammation, and is achieved by providing appropriate drugs and education on exercise and smoking cessation. Since the introduction of tumor necrosis factor (TNF)α inhibitor for the treatment of AS in the early 2000s, treatments

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have developed dramatically. In 2017, an interleukin-17 inhibitor was approved by the Korea Food and Drug Administration for secondary use when TNFα inhibitor proves ineffective [7].

It is paramount for the provision of effective health care delivery that clinicians be familiar with the findings of epidemiologic studies on the prevalence of AS and its associated mortality and disability rates. Unfortunately, no systematic studies have been conducted on the treatment of AS in Korea. Accordingly, we undertook to review the epidemiology and treatment of AS in Korea.

EPIDEMIOLOGY

Prevalence

In a study performed using the Korean Health Insurance Review Agency database (2010 to 2015), the prevalence of AS was found to increase from 31.6 per 100,000 (95% confidence interval [CI] 31.1~32.1) in 2010 to 52.3 (95% CI 51.7~52.9) in 2015, and its incidence increased from 5.7 per 100,000 person-years (95% CI 5.5~5.9) in 2010 to 7.9 (95% CI 7.6~8.1) in 2015. In 2015, the prevalence of AS in male was 83.11 per 100,000 persons, which was 3.6 times higher than the female prevalence (23.16 per 100,000 persons). In the same year, the highest prevalence was reported among medical aid patients, who had three times higher prevalence of other patients (with higher income statuses) [8]. The reported prevalence of AS in Korea is in the lower group in other parts of Asia, in which prevalence reportedly range from 3.0 [9] to 33.7 [10] per 10,000 persons. However, the prevalence of AS in Korea is almost the same as that in Japan, 0.04% [11].

Genetic factors

Genetic factors play an important role in the pathogenesis of AS, especially human leucocyte antigen (HLA)-B27, a class I antigen of the major histocompatibility complex.

Reportedly, about 90% of AS patients are positive for *HLA-B27*, but in healthy general populations, the frequency of *HLA-B27* positivity varies according to race. In addition, the frequency of the *HLA-B27* subtypes and the incidence of AS (regardless of *HLA-B27* status) are also race-dependent [12]. *HLA-B27* positivity rates in Caucasians, North Africans, Chinese, and Japanese were reported to be 7%~8%, 4%, 2%~9%, and 0.1%~0.5%, respectively, and in northern Scandinavia, 24% of the general population were *HLA-B27* positive, but only 1.8% of *HLA-B27* positive individuals had AS [13]. In a study on the frequency of *HLA-B27* in 1,020 Korean adults (902 males, 118 females), 45 (5.0%) males and 2 (1.6%) females were *HLA-B27*-positive, which represented 4.6% of healthy adults [12], and concurs with a reported *HLA-B27* gene frequency in Koreans of 4.6%~6.3% [14].

The *HLA-B27*, B*2705, B*2704, and B*2702 subtypes exhibit strong correlation with AS, whereas other subtypes such as B*2709 and B*2706 do not [15]. A comparative analysis of B27 (+) blood samples from 143 Korean patients with AS and 32 controls showed AS samples were B*2704 (+) in 7.7%, B*2705 (+) in 90.9 %, and B*2710 (+) in 1.4%. Results in controls were B*2704 (+) in 34.4%, B*2705 (+) in 59.4%, B*2710 (+) in 3.1%), and B*2715 (+) in 3.1%, and the B*2705 subtypes percentage was significantly higher in AS patients than controls. No significant differences in clinical features (e.g., peripheral arthritis and uveitis) or laboratory parameters (acute phase reactants) were observed in the B*2704 and B*2705 subgroups [16]. Furthermore, these rates are similar to B*2705 (67.9%, 55/81) and B*2704 (28.4%, 23/81) positivities reported for Indian AS patients [17]. However, B*2704 (80.7%, 105/130) was more common than B*2705 (18.4%, 24/130) in Chinese AS patients [18]. Actually, the B*2704 subtype is mainly encountered in Southeast Asia, e.g., Thailand [19], and Indonesia [20], whereas B*2705 is mainly found in Caucasians [21]. Lee et al. [22] suggested that the predominance of B*2705 in Korean AS patients reflects migrations of Asians from Mongolia and Siberia.

Extra-articular manifestations

According to Korean national health insurance data from 2003 to 2013 of 1,111 AS patients and 5,555 controls, 28% of AS patients developed one or more extra-articular manifestations. The most common extra-articular manifestation was uveitis, which occurred in about 20% of AS patients, and this incidence was more than 9 times than that in the control group. AS patients also showed a higher disability rate than the controls (odds ratio [OR] 5.3, 95% CI 3~6.6), which was higher for severe physical disability. However, no statistical difference was observed between the mortality rates of AS patients and the controls. Furthermore, multivariate analysis showed that male sex, presence of extra-articular manifestations, age at diagnosis, and longer duration of follow-up were independent risk factor for all cause disability [23]. On the other hand, acute anterior uveitis was the most common (11.4%) extra-articular mani-

festation in a UK-based research bank data study conducted from 1987 to 2012 on 4,101 AS patients and 28,591 age, sex and practice matched controls, and its incidence was 20 times higher among AS patients [24]. In meta-analysis, the prevalence of acute anterior uveitis among AS patients was found to be highest in North America (35.2%), followed by Europe (29.3%), Asia (21.4%), and Latin America (20.1%) [25]. Characteristically, in the Hanyang University AS Study of 732 males and 98 females, 1) Korean AS more frequently involved peripheral joints and hip joints, 2) females had a higher incidence of uveitis, and 3) juvenile-onset AS had the higher percentage [26].

Radiologic progression

Ankylosis caused by spinal abnormal bone formation in AS is an important problem that deteriorates the quality of life. Spinal radiologic progression was delayed when AS was accompanied by peripheral arthritis [27]. Spinal radiologic progression occurred more slowly in juvenile onset AS compared to AS in adults [28]. Furthermore, no association was shown between uveitis and spinal radiologic progression in AS [29].

Cardiovascular disease and related mortality

According to a study on chronic heart failure and mortality among 2,988 AS patients and 64,940 age- and sex-matched controls using Korean National Health Insurance Service data from 2010 to 2014, 102 (0.79%) AS patients and 201 (0.32%) controls suffered chronic heart failure. Furthermore, 211 (1.62%) AS patients and 639 (0.98%) controls died during the study period, and AS patients experienced heart failure and had mortality adjusted hazard ratios of 2.38 (95% CI 1.8~2.8) and 1.7 (95% CI 1.4~1.9), respectively, as compared with controls [30]. Furthermore, mortality studies revealed that cardiovascular mortalities are most commonly attributed to AS [31,32]. Standardized mortality in AS patients is 1.6 to 1.9 times higher than in the general population, and among patients, premature mortality is often caused by cardiovascular disease [33,34]. When 1,843 AS patients were compared with age, sex-matched controls in a US study, the prevalence ratio of ischemic heart disease was 1.8 [35].

In a study of cardiovascular disease risk with TNFα inhibitor effect in 450 axial spondylitis patients, there was no statistically significant association between TNFα inhibitor therapy and cardiovascular disease risk reduction [36].

Infection

Regarding infection-associated epidemiologies, a study that investigated incidences of Herpes Zoster using the Korean National Sample Cohort Database from 2002 to 2013 found that the incidence of Herpes Zoster in AS patients was 11.0 per 1,000 person-years. Also, the hazard ratios of Herpes Zoster among conventional disease modifying anti-rheumatic drug (DMARD) s and TNFα inhibitor user after adjusting for sex, age, and baseline corticosteroid were 3.7 (95% CI 9.1~28.0) and 3.5 (95% CI 6.1~27.8), respectively, which was a significant difference. In particular, among patients treated with TNFα inhibitor, the risk of Herpes Zoster increased in females and over 50 years of age, but no difference was observed for steroids [37]. In a Taiwanese study based on a Longitudinal Health Insurance Database from 2003 to 2013, risks of Herpes Zoster were determined among 2,819 AS patients and 11,267 controls and the incidences of comorbidities (e.g., chronic urticaria, inflammatory bowel disease, thyroid disorders, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and cerebrovascular incidents) were higher among AS patients than controls [38].

No significant difference in the severity of infection, pneumonia, and herpes zoster hazard ratio was attributed to TNFα inhibitor type among 2,515 Korean AS patients receiving TNFα inhibitor. On the other hand, the hazard ratio of tuberculosis was significantly higher in the infliximab group than in the etanercept group (adjusted hazard ratio [HR] 8.40 [95% CI 1.1~66.9]) In a subgroup analysis by sex, the HR of herpes zoster was higher in the females treated with golimumab than in the etanercept group (adjusted HR 12.40 [95% CI 1.4~109.6]) [39].

Child-birth and quality of life

One epidemiology study on AS patients examined childbirth-variables by comparting 996 AS patients and 1:10 matched general population females with respect to pregnancy outcomes. The cesarean section rate was significantly higher in the AS patient group (44.4% vs. 20.4%, p=0.002), but no significant intergroup differences were observed for fetal outcomes, such as growth restriction, fetal malformation, and Apgar score [40]. A Swedish study on the pregnancy outcomes of 388 AS patients and matched controls reported emergency and regular cesarean surgery were performed in 16.5% and 9.8% of AS patients, respectively, and in 6.5% and 6.9% of controls, which resulted in OR of 3.0 (95% CI 2.0~4.5) and 1.7 (95% CI 1.1~2.5), respec-

tively [41].

In a study of 211 (161 males) patients with AS in Korea, a higher AS disease activity score indicated a lower quality of life for males and females. For males, employment status was associated with a lower quality of life (OR 0.4, 95% CI 0.2~1.0), whereas disease activity (OR 1.9, 95% CI 1.0~3.4), current smoking (OR 3.0, 95% CI 1.1~8.2), and being employed (OR 0.2, 95% CI 0.1~0.5) were associated with depression. For females, living with one's spouse was associated with depression (OR 0.1, 95% CI 0.01~0.9) [42].

TREATMENT

Treatment trends

Park et al. [43] conducted a study on the treatment trends for AS in Korea from 2006 to 2016 using the Korean National Health Insurance System dataset. The most prescribed drugs were non-steroidal anti-inflammatory drug (NSAID)s, followed by DMARDs, and TNFα inhibitors. Prescriptions for TNFα inhibitors increased from 10% to 35% in 10-year study period. AS regards combination therapy, NSAIDs+DMARDs accounted for 90% of all drug treatments in 2006, but this reduced to 65% in 2016, whereas TNFα inhibitor+NSAIDs usage increased from 3% to 28%. This change in drug usage corresponds to the acceptance of TNFα inhibitor into national insurance coverage [43]. The dose reduction of TNFα inhibitor was found in 17.8% in a two-year retrospective study of 1,352 AS patients and medical costs were reduced by 30% [44].

Patients registry program

AS treatment strategies continue to change in favor of biological agents such as TNFα inhibitors. In 2008, Choi et al. [45] reported that the administration of etanercept for 3 months to 132 AS patients non-responsive to conventional DMARDs achieved excellent results without any serious side effects. However, safety issues such as infections and tumor occurrences made it necessary to initiate a patient registration program to monitor side effects systematically. South Korea also started The KOrean College of Rheumatology BIOlogics and targeted therapy (KOBIO) registry project in 2011 led by the Clinical Research Committee of the Korean Rheumatology Society. Committee members were asked to develop case report forms for rheumatoid arthritis, AS, and psoriatic arthritis, to simplify the systematic collection of data on AS patients treated with biologics [46].

Significant and unreported major side effects such as increased blood creatinine and decreased blood low-density lipoprotein were reported to occur in a drug dependent manner among 1,940 AS patients registered in the KOBIO registry [47]. Discontinuation and switching rates of TNFα inhibitors were 24.2% and 9.6%, respectively, and the most common reason for discontinuation was lack of effect (32.6%) [48]. Predictions of the effects of biologic DMARDs were compared and analyzed using several machine learning models including the random forest method, and a logistic regression model in 611 AS patients. The two methods had similar predictive performances [49].

Biosimiliars

Various types of TNFα inhibitors could be produced in Korea. Currently, the main issues are real-world drug survival, safety, and effectiveness. Drug survival, safety and effectiveness were no different in 337 AS patients induced in the KOBIO registry that switched to CT-P13 (an infliximab biosimiliar) from infliximab up to 5 years [50].

Infection

Using Korean Health Insurance Review & Assessment Service data among 2515 AS patients treated with TNFα inhibitor, the incidence rate of serious infection was 46.65 per 1,000 person-years (95% CI 39.70~53.60), and no significant difference was observed for different TNFα inhibitors. The incidence rate of tuberculosis was 4.90 (2.70~7.10) per 1,000 person-year, and the adjusted hazard ratio of the infliximab group was significantly higher than that of the etanercept group (8.40 [95% CI 1.06~66.91]). Furthermore, females group treated with golimumab had a significantly higher Herpes Zoster hazard ratio than those administered etanercept (adjusted HR 12.40 [95% CI 1.40~109.58]) [39].

In general, if active tuberculosis occurs while treating AS patients with a TNFα inhibitor, anti-tuberculosis drugs are administered, and conventional DMARDs are administered after the TNFα inhibitor has been discontinued. However, according to the retrospective registry of Korean Society of Spondyloarthritis Research, it is safe to take antituberculosis drugs and resume TNFα inhibitors when active tuberculosis develops Twenty-three AS patients developed active tuberculosis during TNFα inhibitor administration. After administration of antituberculosis drugs, TNFα inhibitor treatment was resumed within 9

months. Tuberculosis was successfully cured and no disease flare-up occurred [51].

Radiologic progression

Characteristic lesions of the skeletal system in AS include ectopic new bone formation and syndesmophytes formations [52,53]. Ectopic new bone formation may impair spinal mobility, and limit daily activities and reduces quality of life [54,55]. Therefore, suppressing skeletal damage in AS is an important treatment goal. Furthermore, it has been reported that conventional DMARDs cannot retard radiologic progression in AS patients [56].

Studies conflict as to whether ectopic bony progression in AS can be inhibited by anti-TNFα therapy. Early large-scale clinical studies showed that anti-TNFα agents could not inhibit bony progression [57-59]. These studies compared patients treated with anti-TNFα agents during clinical trials and the patients with spinal X-rays stored in the cohort without anti-TNFα agents during same period. These studies compared patients treated with anti-TNFα agents during clinical trials and the patients with spinal X-rays stored in the cohort without anti-TNFα agents during same period. However, two recent long-term studies conducted by Korean researchers have reported that anti-TNFα agents inhibit ectopic bony progression [60,61]. In a retrospective study of AS patients who received TNFα inhibitor treatment at least once from 2001 to 2018, the modified Stoke AS Spinal (mSASS) scores obtained during TNFα inhibitor administration showed much less change when TNFα inhibitor was not administered [60]. In the other Korean study, changes in the mSASS score were obtained over 4 years. Of the AS patients enrolled, 135 received a TNFα inhibitor and 80 NSAIDs, and it was found that changes in mSASS score were less in those that received a TNF inhibitor (β=−0.90 [95% CI −1.51 to −0.29]) [61].

CONCLUSION

Several studies have evaluated the epidemiology and treatment of AS in Korean patients. Reports show the prevalence of AS is lower in Korea than elsewhere in Asia, except Japan. The reported frequency of *HLA-B27* in Koreans is 4.6%, and the B*2705 subtypes ratio is significantly higher in Korean AS patients than in normal controls. The most common extra-articular manifestation was uveitis. In Koreans, AS was found to more frequently involve peripheral joints and hip joints, be associated with uveitis in females, and have a higher juvenile-onset percentage. No significant difference was observed between each TNFα inhibitors in terms of the severity of infection, pneumonia, and herpes zoster hazard ratio. It was possible to systematically collect much data on AS patients treated with biologics from the KOBIO registry. Drug survival, safety and effectiveness were the same in patients switched to infliximab biosimiliars from infliximab. Furthermore, it is safe to administer anti-tuberculosis drugs and resume TNFα inhibitors when active tuberculosis develops. Moreover, recent long-term studies have reported that anti-TNFα agents inhibit spinal radiologic progression. More research is needed by rheumatologists passionate about the epidemiology and treatment of Korean AS patients.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

S.-R.K. conceptualized the study. T.-H.K., T.-J.K, W.P., and S.C.S performed data acquisition. S.-R.K. wrote the manuscript.

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