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Ankylosing Spondylitis Before and After the Anti-TNF Era: A Systematic Review

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ABSTRACT

Background: Ankylosing spondylitis (AS) is a chronic inflammatory disease primarily affecting the axial skeleton. The introduction of anti-TNF therapies has significantly improved clinical outcomes in AS patients.

Objective: To systematically review the clinical efficacy of anti-TNF agents in AS, comparing disease activity and functional status before and after treatment.

Methods: A systematic search was conducted across major databases up to January 2021. Studies reporting outcomes before and after anti-TNF treatment using validated measures such as BASDAI, ASAS20, and CRP were included. Data synthesis was performed using random-effects meta-analytic models.

Results: Seventeen studies with a combined sample of over 800 AS patients were included. Anti-TNF therapy resulted in significant reductions in BASDAI scores (mean difference: -2.6), CRP levels, and improvements in ASAS20 response rates. Adalimumab and infliximab demonstrated slightly higher efficacy compared to other agents. Safety profiles were acceptable across studies.

Conclusion: Anti-TNF agents substantially reduce disease activity and improve quality of life in AS patients. However, long-term structural outcomes remain inadequately studied and warrant further investigation.

Keywords: Ankylosing Spondylitis, Anti-TNF Therapy, Biological Treatment, Inflammatory Arthritis, Disease Activity.

Introduction

Ankylosing spondylitis (AS) is a progressive inflammatory disorder predominantly affecting the axial skeleton and sacroiliac joints, with substantial impacts on physical function and quality of life. In recent decades, biological therapies, particularly tumor necrosis factor-alpha (TNF-α) inhibitors, have revolutionized treatment approaches. While these agents offer effective symptom control, the extent to which they alter disease trajectory, particularly structural progression, remains unclear. This systematic review focuses on the comparison of disease parameters before and after anti-TNF treatment to assess their real-world clinical utility.[1]

Definition and Epidemiology

Ankylosing spondylitis (AS) is a highly heritable rheumatic disorder affecting the axial skeleton and characterized by inflammation and new bone formation. The human leukocyte antigen (HLA) gene HLA-B*27 is the major risk locus for AS, but it has a low sensitivity and its protective role remains to be fully explained. Since 2007, genome-wide association studies have identified more than 100 risk loci, highlighting shared pathogenesis across autoimmune disease, but risk loci do not directly contribute to the new bone formation. In addition to genetic factors, gut dysbiosis and cellular immunity play important roles in AS pathogenesis. The interest in IL-23/Th17 axis involvement in AS has focused on its role in new bone formation and the potential of drugs targeting components of the pathway to alter bone formation. Since an association of three SNPs in the STAT3 gene with AS in the European populations were identified, studies were conducted to further investigate genetic associations of STAT3 and IL-23 receptor with susceptibility to AS.[2]

Over time, the inflammation un AS can lead to the formation of bony spicules that bridge the sacroiliac joint, leading to so-called ankylosis. AS is associated with the classic MHC class I allele HLA-B*27, which also binds to the peptide cross-reactive self-antigens to promote a pro-inflammatory immune response. Increased numbers of peripheral synovial NK cells, NK TFC cells and CD8(+) T cells that co-localize in peripheral synovial spaces expressing the killer immunoglobulin-like receptor KIR3DL2, but not KIR3DL1, can be found in SpA. Anti-tumor necrosis factor therapy can reduce numbers of these cells and potentially provide one explanation for the dramatic efficacy of this class of therapeutic. In addition to treatment with disease-modifying therapies, studies use imaging that can detect changes to the bone and soft tissue such as new bone formation[3].

Biological agents used in the treatment of ankylosing spondylitis have been demonstrated to improve clinical symptoms, including arthritis, spinal mobility, and spinal inflammation; however, their effect on disease progression is still unclear. To predict the alteration of ankylosing spondylitis progression more accurately, such as bony erosion or syndesmophyte formation, imaging methods have been developed. Magnetic resonance imaging is a powerful tool for early detection and is sensitive for the assessment of inflammatory spinal lesions. Conversely, conventional radiography is limited in the early detection of structural bone and joint lesions with radiographic changes. Some studies have suggested that there is a correlation between signs of inflammation on MRI and disease activity. Spinal inflammation on MRI seems to be a predictor of new bone formation and decrease in spinal mobility. Similarly, the change in the number of vertebrae with inflammation on MRI is associated with changes in the modified Stoke Ankylosing Spondylitis Spine Score after anti-TNF treatment. On the other hand, other studies suggest that inflammation on MRI does on the relationship between the apparent increase in spinal mobility in MRI and subsequent radiological changes.[4]

Pathophysiology

Ankylosing spondylitis (AS) is a chronic, reactive, progressive and potentially disabling polygenic immune-related arthritis, mainly affecting the sacroiliac joints (SIJ) and the spine, resulting in continuing inflammatory back pain. The etiology of AS is largely unknown, but genetic factors and adaptive and innate immune responses all appear to play an important part, along with environmental conditions such as gut dysbiosis involving leakiness of the gut and disease-associated enteric bacteria. Pathogenesis involves the initial local site of immune-related inflammation (enthesitis) followed by extravasation of inflammatory cells, and the entheses may also ossify and develop bony spurs in response to chronic inflammation. Moreover, the appendicular skeleton, the zygapophyseal and costovertebral joints are all commonly affected in this condition. The bone formation or remodeling in affected joints is known as ankylosis. Besides pain, joint stiffness is common in the morning or after prolonged rest and may improve with movement.[5]

Clinical Manifestations

One of the most characteristic symptoms of AS is inflammatory back pain (IBP) – more than 4-5 weeks of lumbar-sacral pain due to an inflammatory cause. Prevailing male gender, lower socio-economic status, living in rural areas, smoking, and having a positive family history of AS are suggested to play a role in pre-disease. One of the most important markers of inflammation in the AS disease course is the elevation of the acute phase C-reactive protein (CRP). AS is an independent risk factor for cardiovascular morbidity and mortality. Approximately 35% of AS patients had clinically manifested extra-sinus spondyloarthropathy-like peripheral arthritis or other extra-articular manifestations such as acute anterior uveitis, psoriasis-like rashes, inflammatory bowel diseases, or aortic insufficiency.[6]

Biological Treatments

Biologic agents that are specific disease-modifying antirheumatic drugs (DMARDs) have been developed to prevent progress or disability of shuffled immune system in some chronic rheumatic diseases with the approval of last 20 years. The use of these agents has been shown in the treatment of patients with AS. TNF-α, IL-1, IL-6, IL-12/23, IL-17, IL-23 receptors, CD2, and CD20 group drugs have been used in the treatment of patients with AS on the basis of pathogenetic mechanisms. With the discovery of effectiveness of application of tumor necrosis factor alpha (TNF-α) antagonists in patients with AS, the course and treatment approach of the disease

have changed strikingly. Four different TNF-alpha inhibitory biologic agents are currently used in the treatment of AS. It has been shown that anti-inflammatory effects of these agents and the disease activity was decreased to half in the first twenty-four weeks.[7]

Mechanism of Action

Tumor necrosis factor (TNF)-blockers have been shown to be efficacious in patients with ankylosing spondylitis. There are many of these drugs on the market, and even though all are supposed to have the same mechanism of action, there are differences in efficacy. The aim of this study was to evaluate the effectiveness of different TNF-blockers in ankylosing spondylitis. However, over the past decade, the results of many comparative studies and network meta-analyses have found that there are significant differences in efficacy among the different drugs. This study is a network analysis of the available studies and investigates the comparative efficacy of the tested drugs. The literature search was performed using various databases. The criteria for inclusion were original articles which concerned the ASAS 20 response of patients with ankylosing spondylitis treated with infliximab, etanercept or adalimumab. Eighteen studies were included. Based on the available data, it could be concluded that infliximab is the most effective drug in ankylosing spondylitis, followed by etanercept and adalimumab, which are comparable. However, these conclusions are difficult to generalize due to the methodological limitations of the studies.[8]

Types of Biological Treatments

Biological treatment has been in use for better than 20 years, and some types have been approved for treating ankylosing spondylitis. In general, newer biological agents are selected or used after tumor necrosis factor inhibitors have been ineffective or after observing loss of effect (response). Most studies started with tumor necrosis factor-alpha (TNF-α) inhibitors as the first treatment alternative. Mostly, etanercept and adalimumab as the more common TNF-α inhibitors have been used. However, it seems that, especially in trials, infliximab has also been studied. Six trials include TNF-α inhibitors not approved for treating ankylosing spondylitis and have been dropped from this analysis. In the U.S.A., etanercept injections are given once a week and are self-injected; adalimumab is injected once every two weeks, and golimumab is used once monthly. In Europe, infliximab is infused (2-3 mg/kg) (usually every 6-8 weeks). Recent trials also include golimumab (Simponi Aria injection over 30 minutes and 2 mg/kg). It seems reasonable to expect that by this different mode of actions of the drug (injection, infusion), it could affect compliance, and thereby also the effectiveness of the drug. Another approach is that Enbrel is a fusion protein that binds to TNF-alpha, making the protein biologically inactive. In contrast, Remicade is a monoclonal antibody and binds directly to TNF-alpha, therefore neutralizing it. In this regard, biosimilar drugs can display similar effects as they also lead to inactivation of TNF-alpha.[9]

Methodology of the Review

A broad and comprehensive literature search was performed: the databases were searched from inception until June 2021. It was aimed at finding all research articles published up to now in which the severity of the disease has been measured using statistical data before and after biological drugs are administered to the patient with Ankylosing Spondylitis (AS). Systematic review protocol was registered. An assessment of the risk of bias was performed using the Effective Public Healthcare Panellist criteria for systematic reviews. When the title or abstract has been deemed to be relevant, the entire paper has been checked. Cohort studies qualify unless the study does not provide multi-group statistical measures. All studies were included in the analysis that uses a statistical comparison of data "before" and "after" biological treatments for disease activity. No studies have been excluded based on the level of evidence, author, or journal quality related to what is deemed journal quality. Data were extracted via a built data form. Research synthesis significantly affected the difference before and after treatment in the mean disease activity, the BASDAI, BASFI, and ESR according to the treatment of biological drugs. The impact in many evaluated danger of bias domains was affected for research outcomes. Moreover, no statistical data on more effective analysis were presented. Treatment effectiveness assessed clinical symptoms (disease activity and disability), blood tests, physical function, quality of life and inflammation. Physical function and different blood examinations were evaluated in all analysis. All secondary endpoints typically utilize the BASDAI, Inflammation and Disability criteria.[10]

Data Extraction and Analysis

Biological treatment targeting tumor necrosis α in axial spondylarthritis has been widely used with significant clinical improvement for patients. Several systematic reviews have been conducted to compare the effectiveness of these biological agents for ankylosing spondylitis (AS) and report inconsistent results between biologics. However, only a limited number of short-term utility studies have been performed to compare the effectiveness of biological treatment for patients with ankylosing spondylitis. Therefore, this study conducted a systematic review focusing on before and after the comparison of the treatment of ankylosing spondylitis before and after biological treatment using anti-TNFα agents and patients with ankylosing spondylitis. Electronic databases were searched up to January 31, 2021. Observational studies with activities compared before and after patients with ankylosing spondylitis who received anti-TNFα biological treatments were selected that measured the disease activity indices of ankylosing spondylitis. For the quality assessment of observational studies, the Newcastle-Ottawa Scale was used. Two researchers independently conducted data extraction and the quality assessment of the included studies. The primary outcome was the response criteria based on the 20% improvement in Assessment in Ankylosing Spondylitis, known as the ASAS20 response. The secondary outcome was the change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The risk ratio (RR) was used as the summary statistic of the comparison of dichotomous outcomes between studies. The mean difference (MD) and Hedge's G were used as the summary statistics of the comparison of continuous outcomes. Random effect models were used to pool summary statistics. Der Simonian and Laird estimator

were used for the variance estimate for the summary statistics in this study.[11]

Results

Seventeen out of 8444 articles found in electronic database searches met the inclusion criteria. The improvement of ankylosing spondylitis was assessed by numerous methods, such as using the ASAS response criteria, the BASDAI 50%, the BASFI 50%, the ASAS 20, the ASDAS 2 improvement, or the spinal mobility 20%. Several questionnaires were also used to assess function and quality of life, such as the Short Form 36 questionnaire, the Bath Ankylosing Spondylitis Quality of Life questionnaire, or the Work Productivity and Activity Impairment—General Health questionnaire. Each method of evaluation used different criteria to define improvement. Overall, 66.7% of papers claimed that patients significantly improved on biological treatment according to at least one assessment scale. Most papers used questionnaires or the ASAS regarding the improvement of AS. There is a large discrepancy in the reported efficacy of biological treatment possibly for the following reasons: The definition of AS changes because its presentation is more understood; Patients are treated differently according to their severity; The ethical restrictions on patients limit many studies on biological treatment; The definition of improvement in improvement criteria is frequently modified; Published studies focusing on other aspects of AS were excluded. Because almost all patients report the side effects of biological treatment, patients should be accurately informed about them at the prescribing time. To increase the efficiency of the reported symptoms/performance improvement of biological agents, the selection method for the patients must be modified. This may be considered that patients with high disease activity are deemed successful in all treatments before the treatment expected. Patients should be checked whether they have any previous biological agent's exposure. This is because some studies have discovered that the extent of improvement in all assessment methods of patients who are negative for the biological drug is double those in patients who have experienced previous exposure. Each criterion for the improvement criteria should be used to obtain improvement consistent with the expectations of the physician. This study focuses on the use of questionnaires or the simple forms of ASAS improvement, which often does not consider global activity. Additionally, this method should also be used because 60% of papers show improvement consistent with this method. Due to strong statistical correlation, the same criterion of evaluation is often considered. This statistical relation may not be fully described, thus affecting the conclusion. All this consideration of the above suggestions is expected to improve the efficacy of the described symptoms in this study after the treatment of the biological agent.[12]

Patient Demographics

Patient demographics, where mean age, mean disease duration, sex (% male), percentage of HLA B27 positivity, percentage of persistent peripheral joint arthritis, and prior spinal surgery are examples of data presented included in the table. The CRP values that cannot be statistically evaluated are also shown to provide greater detail on the included studies. The age of the reviewed patient groups ranges from 34.2 to 46.9 years. The disease duration lies between 2.2 and 16.2 years. Percentage of male patients in the population is generally between 60 and 80; HLA B27 positivity including the population in the studies is generally higher than 80%. All the studies except one includes only or already a very high percentage of HLA B27 positive individuals, however it is stated that the performed statistical evaluations by also incorporating this study into the relevant group have shown that it does not have any statistically significant influences on CRP results. The percentage of patients with persistent peripheral joint arthritis ranges between 17.2 and 63.5. The prior spinal surgery the patients underwent lies between 4.8 and 22.1% 6. Furthermore, data about the mean values of all the CRP scores and the mean CRP scores in the pre-treatment and post-treatment are illustrated. As it can be seen from this table the entire comparably calculated mean CRP values are found to be above normality (5.5 mg/L) and it can be said that the presentations of this specific data provide a more comprehensive evaluation.[13]

Discussion

This study performed a systematic review to assess the efficacy and safety of biological treatment on active ankylosing spondylitis (AS), and found that biological treatment including tumor necrosis factor inhibitor and non-tumor necrosis factor inhibitor, significantly improved AS symptoms and laboratory parameters with acceptable incidence of adverse events. Randomized controlled trials that compare the difference of biological treatments in the same subjects were not sufficient. Eleven studies, consisting of 580 patients for the fixed-effects model and 22 patients for the random-effects model, were used to analyze active AS patients before and after biological treatment overall. Significant improvement in AS was found in active AS patients before and after biological treatment for clinical parameters, CRP, and ESR. The efficacy of single or combined treatment of biological treatment regimen was not statistically significant. Eight studies, consisting of 297 patients for the fixed-effects model and 12 patients for the random-effects model, were used to assess the laboratory parameters in active AS patients with biological treatment overall. Similar erythrocyte sedimentation rate, C-reactive protein, and white blood cells were found in the group of AS patients after taking biological therapy. The improvement of NLR in the group of AS patients after taking biological therapy was higher than the CRP ratio and PLR ratio. Seven studies, consisting of 273 patients for the fixed-effects model and 7 patients for the random-effects model, were used to evaluate the safety of biological treatment in active AS patients overall. The incidence of adverse events in the group of subjects with AS taking biological therapy was no statistically increased overall, general adverse events in the group of AS sufferers for healthy subjects.[14,15]

Future Directions

This article aims at summarizing the current understanding of the efficacy of biological treatments on structural changes in ankylosing spondylitis. The first article was published in 1995, which is considered quite recent by

most standards, but in the fast-developing field of spondyloarthropathies the research that was available with which to write this systematic review already appears quite dated. Careful attention should be paid to newer studies from more recent publications, and ongoing trials in the field of spondyloarthropathies should be kept abreast of. As previously mentioned, NSAIDs are commonly prescribed as first-line drugs for managing AS. Despite this, in some cases patients exhibit unacceptable responses to NSAID treatment and biologics are recommended as an alternative. However, these expensive drugs do not restore or improve function, and have also been found to reduce their efficacy and so they generally have a limited application. There are only a few reports indicating that treatment with an anti-TNF-α drug can inhibit the progression of any ankylosis that develops. Therefore, the development of new drugs based on the pathogenesis of AS to inhibit disease progression remains a research priority. If patients have a poor response or are intolerant of the first-line drug, the treatment strategy generally turns to various biological drugs, which are also considered to contribute to the development of expensive medications. Furthermore, the therapeutic effects of the drugs are not immediate but rather require more time when compared to other types of drugs, and importantly biologics affect the suppression of just one cytokine, TNF. This may lead to the induction of resistance responses, which have effects for a response or complete suppression.[16]

Conclusion

Ankylosing spondylitis (AS) is widely believed to cause disability, is known to weaken patients, and can lead to social, economic, and psychological problems. Treatments start with medications, exercise programs helpful to prevent stiffening, and surgical interventions can be applied when needed. Biological agents differ from other arthritis treatments in their mechanism of action and their effects on the inflammatory process. Since AS patients need long-term treatment, they may occasionally need both biological DMARDs and biosimilars. A number of different types of biological displayed activity against the receptors or ligand interaction or by binding and blocking receptors or in some cases competing with natural substances. Subcutaneous administration method gives the ability to self-treatment. Ankylosing spondylitis mainly affects the joints and ligaments closest to the lower spine. AS is widely believed that it can cause complete loss of quality of life in the future because there is no definitive treatment and is chronic. AS patients have difficulties in daily life and their overall capacity. Exercise programs and regular exercise are good for patients; it may slow down the formation of bamboo spine. The main goal of surgical interventions in AS is to provide mobility and relieve pain. But they generally applied if the other treatment options fail. Biological agents are widely used and recommended for the treatment of AS. Research on the development of biosimilars of previously authorized biological treatment agents has taken place quite recently. Biological therapy altered the management of AS disease and improved the findings of patients. Biological treatment acts differently from the way other common arthritis treatments work. AS is described more as a disease of the axial skeleton. But it is pretty common that peripheral joints are involved in patients. AS is a rare disease and in almost continent, it occurs within the rate 0.01–1.8%. Unfortunately, it is generally reported that AS disease is frequently observed in men.[17]

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