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ELEVATED SERUM LEVELS OF IL-17 DURING DISEASE ACTIVITY OF ANKYLOSING SPONDYLITIS: A SYSTEMATIC REVIEW WITH META-ANALYSIS

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Abstract: Concentrations of serum IL-17 have been found at high levels in patients with AS. The role of serum IL-17 in ankylosing spondylitis (AS) was investigated through a meta-analysis undertaken to examine the correlation between AS disease activity and serum levels of IL-17 in AS compared to healthy controls and AS patients. Searches were performed in PubMed, ScienceDirect, Cochrane, and Lilacs databases for pertinent case-control studies using with the descriptors "Spondylitis, Ankylosing" and "Interleukin-17". Expression in relation to healthy controls and correlation of IL-17 with BASDAI were plotted using Review Manager 5.3 software. Quality assessment of each eligible study used the Newcastle-Ottawa Scale. Thirteen case-control studies were selected for this meta-analysis and contained a pooled total of 752 AS patients and 607 healthy controls. Our main result revealed strikingly higher levels of serum IL-17 in AS patients, compared to healthy controls. Pooled mean difference 14.59, pooled risk ratios (RRs) with 95% confidence intervals (CIs) 7.73, 21.45; $p<0.00001$. Serum IL-17 is highly expressed in serum of patients with AS and is related to disease activity. The treatment in use significantly influenced IL-17; however, we did not observe a significant difference in the expression of IL-17 in the treatment of patients taking anti-TNF, proving that it does not interfere in this pathway.

Keywords: Case control studies, expression IL-17, IL-23 and IL-17 pathway.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, inflammatory disease of the axial spine that can manifest with various clinical signs and symptoms (WENKER; QUINT, 2021; BRAUN, 2007). Current treatments aim to reduce symptoms, maintain spine flexibility and normal posture, and reduce limitations and

complications while maintaining work ability (WARD, 2016; SIEPER, 2019). The choice of treatment is based on remission or low disease activity accompanied by laboratory tests (SMOLEN et al., 2013). Non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biological DMARDs (bDMARDs), and physical activities are recommended (TAM et al., 2019).

Anti-TNFs play a key role in blocking AS, significantly reducing inflammation and bone destruction (TAUROG; CHHABRA; COLBERT, 2016). Current findings indicate participation in the IL-23/IL-17 pathway in the pathophysiology of AS (DEVECI, 2020; SHERLOCK; BUCKLEY; CUA, 2014; HREGGVIDSDOTTIR; NOORDENBOS; BAETEN, 2013). The IL-23/IL-23R complex in predisposed patients appears to induce the activation of signal transduction and transcription, with consequent proliferation and terminal differentiation of Th17 cells, resulting in the production of IL-17 (SHERLOCK; BUCKLEY; CUA, 2014; SMITH, COLBERT, 2014; ZUNIGA, 2013; MCGEACHY, 2009), TNF-α and other proinflammatory cytokines, and chemokines (YEREMENKO; PARAMARTA; BAETEN, 2014).

However, the literature diverges as to the expression of IL-17 in serum of EA patients, and this may be related to the treatment used by the patient. Hence, we undertook a meta-analysis to investigate how the disease activity and influence of the treatments used is related to the expression of IL-17 in the serum of EA patients.

METHODOLOGY

Our report adheres to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Statements (STROUP et al. 2000). All enrolled studies satisfied the following criteria: (1) all AS patients conformed to the New York clinical criteria for AS (van der LINDEN; VALKENBURG; CATS, 1984); (2) was a cross-sectional or case–control study; (3) reported the correlation between serum IL-17 levels and AS; (4) included AS patients as case group and healthy controls as control group and/or patients who are not active. The exclusion criteria were: (1) inconsistent diagnostic criteria for AS; (2) not case-control studies; and (3) incomplete original data.

The following electronic databases were consulted: Pubmed, ScienceDirect, Cochrane, Lilacs published until November 2019. The basic research strategy included "Spondylitis, Ankylosing" and "Interleukin-17". There was no language restriction. References to selected articles were reviewed to identify all relevant studies. Relevant data were independently extracted by two reviewers, and disagreement was resolved by a third reviewer. The data were collected from each study.The Newcastle–Ottawa Scale (NOS) was performed to blindly assess the methodological quality of the case–control studies by two reviewers.

STATISTICAL ANALYSIS

The difference in serum IL-17 levels between the case and control groups and patients who were not active was compared by mean difference (MD) with 95% confidence intervals (95% CI), and the correlation between serum level and disease activity in AS was performed by CORs with 95% CI. The significance of clustered MDs and CORs was determined by the Z test and $p<0.05$ was considered statistically significant. Cochran's Q-statistic was considered significant with $p<0.05$ and I2 tests were applied to determine heterogeneity. We quantified the effect of heterogeneity by using a recently developed measurement, namely, $I2=100\% \times (Q-df)/Q$, *with values of 25%, 50%*, and 75% indicating low, moderate, and high heterogeneity,

respectively. The parameters of enrolled studies were mean ± SD. The interquartile was calculated for the studies that did not have the standard deviation. All statistical analyses were carried out in RevMan software.

RESULTS

ELIGIBLE STUDIES SELECTED FOR META-ANALYSIS OF SERUM IL-17 LEVELS AND AS

The systematic review conducted in November 2020 of studies with IL-17 cytokine in serum of AS patients found 13,472 articles in Pubmed, ScienceDirect, Cochrane, and Lilacs databases (Figure 1). After the removal of duplicates, 12,498 articles remained. By reading titles and abstracts, the list was reduced to 69 articles. After analyzing the texts in full, 13 were selected for the meta-analysis, according to the inclusion criteria previously established.

The thirteen studies selected for meta-analysis contained a combined total of 1359 patients with AS and 746 healthy controls. Sample sizes in the studies ranged from 23 to 143 AS patients. All were published in English language excerpt the study from Russia. The main characteristics of the studies are presented in Table 1.

META-ANALYSIS RESULTS FOR SERUM LEVEL OF IL-17

Of the 13 articles selected, only 8 found statistical significance ($p<0.05$) of patients' IL-17 expression in relation to healthy controls (Figure 2). A total of 3 articles reported the correlation of IL-17 with disease activity Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (Figure 3). Our meta-analysis observed the existence of heterogeneity in the 13 studies published in the random effect model used ($I2=99\%$, $p=0.00001$). As a main result, we observed that IL-17 expression is higher in patients than in controls (MD=9.75, 95% CI=6.43~13.07, $p<0.00001$). Nine studies found a correlation of BASDAI disease activity with serum levels of IL-17 (MD=14.59, 95% CI=7.73 ~ 21.45, $p<0.00001$).

We evaluated studies with patients with and without activity (MD=0.37, 95% CI=-2.19 ~ 2.93, $p=0.87$, $I2=0\%$) and before and after treatment (MD=46; 95% CI=-15.79 ~ 32.71, $p=0.02$, $I2=74\%$) (figure 4).

When the treatments were analyzed, the IL-17 expression of the untreated patients was higher than those treated with conventional drugs, with the average difference of MD= 23.70, 95% CI = 4.60 ~ 42.79, P = 0.02 and MD= 10.24, 95% CI = 3.32 ~ 17.17, $p=0.004$, respectively. Patients using IL-17 did not show significance in relation to controls (Table 2).

SENSITIVITY ANALYSIS AND RISK OF PUBLICATION BIAS

Only four studies had a weight lower than 7% (figure 3). The risk of bias in the studies was performed in the RevMan program and according to the Newcastle-Ottawa Scale (NOS) criteria (Figure 5).

DISCUSSION

In this study, we undertook a meta-analysis based approach to investigate the significance of elevated serum levels of IL-17 in AS development and the influence of conventional and anti-TNF drugs on cytokine expression. The serum IL-17 values in AS expression diverge greatly between articles. The studies showed that serum levels of IL-17 in AS patients were significantly higher than those of healthy controls. However, many case-control studies performed in different countries obtained conflicting results. This can be related to high heterogeneity index between studies.

Our main results found serum levels of IL-17 strikingly higher in AS patients than healthy controls, indicating that the cytokine

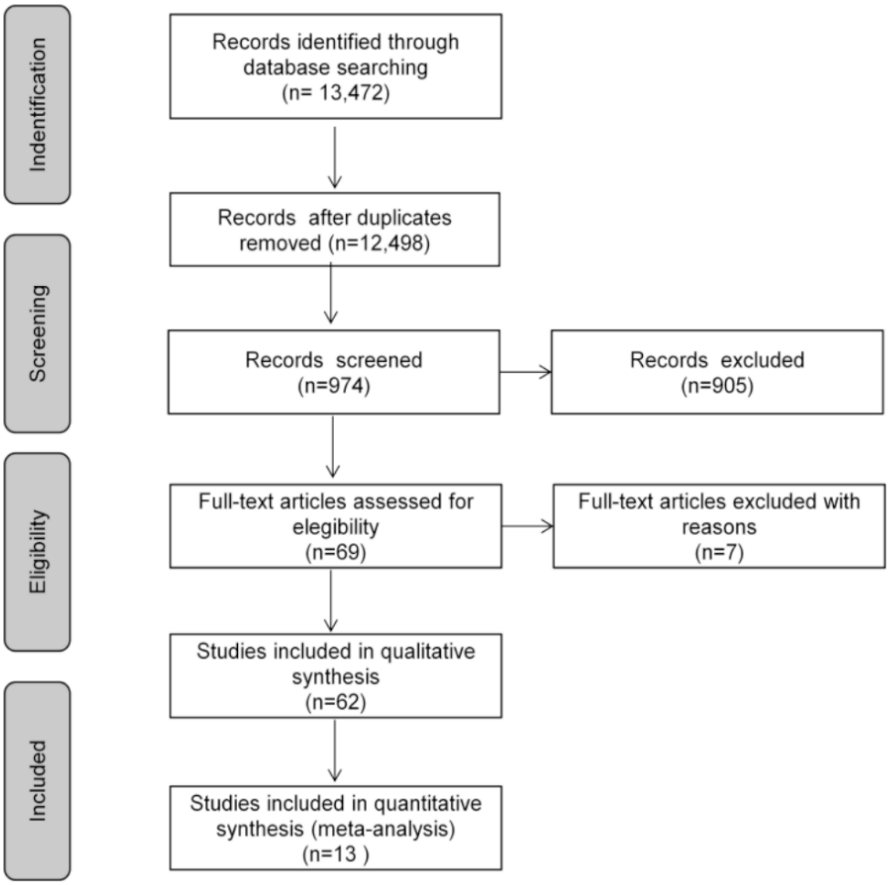

Figure 1. Flow diagram of the study selection process.

First author, year, reference	Country	Type of research	Ethnicity	CASE							CONTROL		
				N	Gender (M/F)	Mean/SD age (years)	Duration of disease (years)	BASDAI mean/SD	C-reactive protein (mg/L)	ESR mm/h	N	Gender (M/F)	Mean age (years)
Chen, 2012	China	Case-control	Asian	49	43/6	39.0±12.3	-	4.47±1.9	15.08±13.2	25.35±24.0	25	-	-
Fattahi, 2018	Iran	Case-control	Caucasians	30	22/8	22/8	11.8±8.6	5.8±1.3	-	-	15	11/4	11/4
Gaydukova, 2017	Russia	Case-control	Caucasians	30	22/8	38.35±9.19	11.4±9.6	6.6±3.29	12.3±3.9	19.3±6.7	20	12/8	40.1±7.7
Han, 2011	China	Case-control	Asian	89	89/0	38.27±9.70	-	3.48±0.89	32.81±17.21	42.23±20.94	178	178/0	39.67±7.1
Inova, 2016	Bulgaria	Case-control	Caucasians	77	59/18	38±10	12±8	-	24.29±2.89	30±22	48	37/11	39±11
Limon-Camacho, 2012	Mexico	Case-control	Caucasians	39	38/8	32±13	17±2	4.4±2.4	14±3.2	-	20	-	32±8
Madej, 2015	Poland	Case-control	Caucasians	49	35/14	40,6±13,4	-	4,8±2,6	24,6±36	30±24	19	-	40,4±10,4
Mei, 2011	China	Case-control	Asian	50	41/9	28.1±8.9	-	3.3±2.1	22.5±8.2	39.1±11.6	43	35/8	25.3±6.7
Milanez, 2016	Brazil	Case-control	Caucasians	47	35/11	38.0±11.1	10.8±4.5	-	29.71±39.56	29.70±23.32	47	-	-
Rabelo, 2018	Brazil	Case-control	Caucasians	32	19/13	46.9±10.7	18 (10–31)	3.9±2.1–6.3	-	-	32	19/13	-
Sohn, 2018	Korea	Case-control	Asian	55	55/0	37.8±10.8	6.48±4.3	4.2±2.2	0.26(0.08-0.7)	15±17.77	26	26/0	35.6±6.8
Sveaas, 2015	Norway	Case-control	Caucasians	143	88/55	49.3±11.0	23.7±11.3	-	3 (1, 10)	15±3.7	124	74/50	53.2±11.3
Wendling, 2008	France	Case-control	Caucasians	23	18/05	39.9±2.1	10.1±1.3	44.1±4.1	22.3±4.7	27.8±5.3	21	-	41.2±2.7

Table 1. Characteristics of the studies included in the meta-analysis

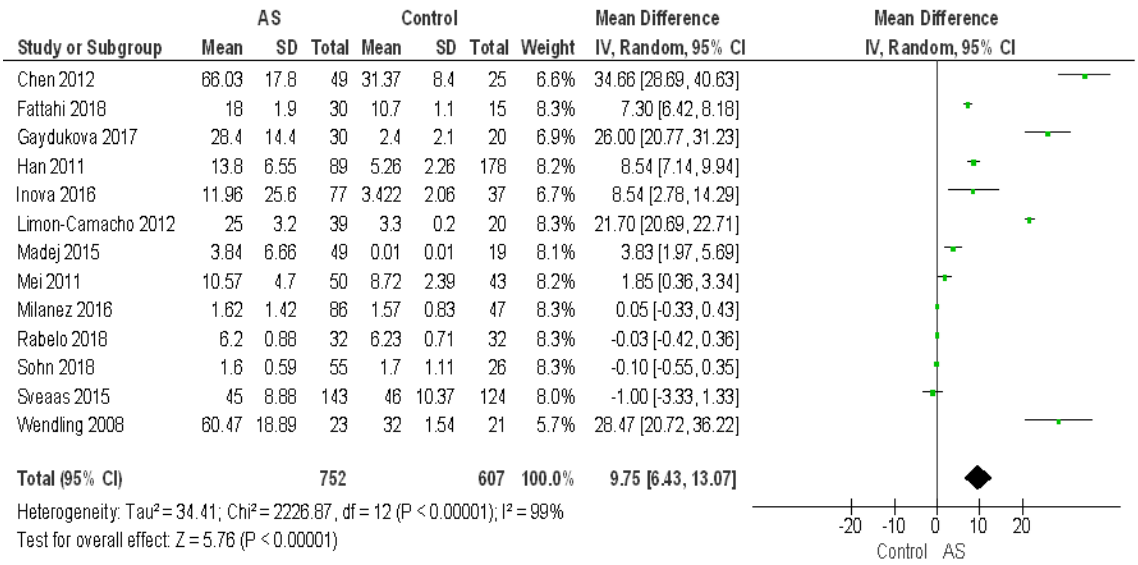

Figure 2. Forest plots IL-17 serum levels in patients AS and controls

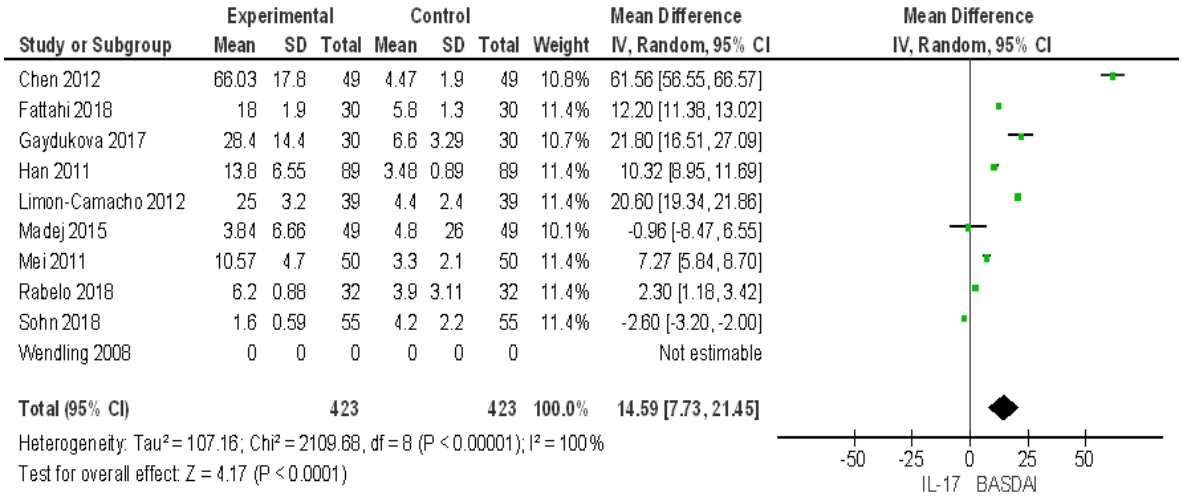

Figure 3. IL-17 serum levels correlation with disease activity (BASDAI)

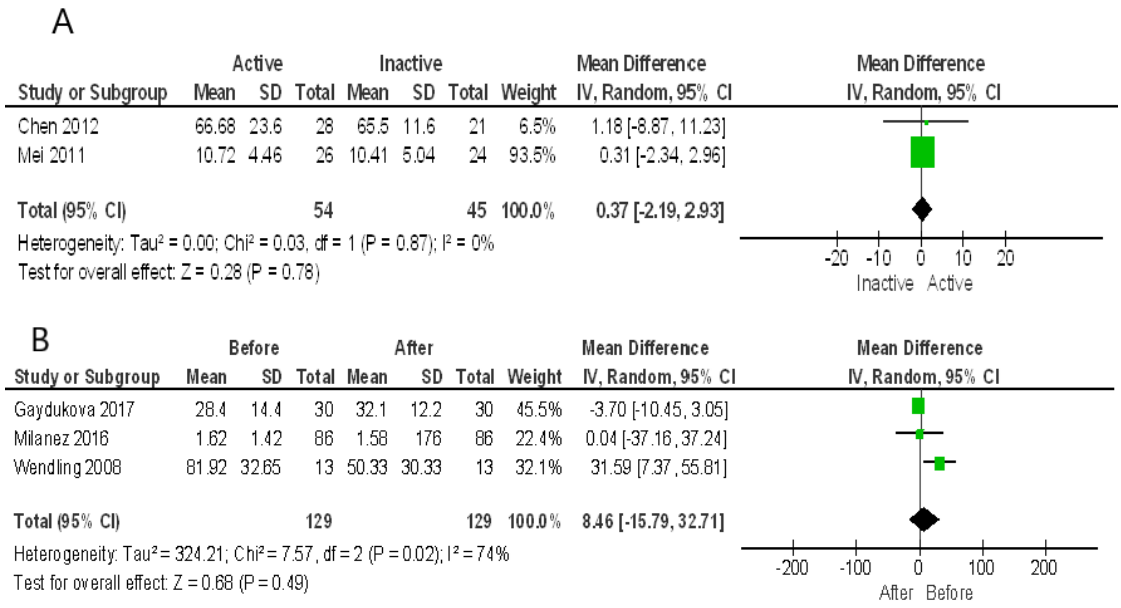

Figure 4. IL-17 serum levels in patients AS: (a)between AS and active/inactive; (b)before and after treatment with anti-TNF

Treatments	Eligible studies	Participants	MD (95%CIs)	P-value	Heterogeneity test	Effect model
Untreated	3	385	23.70 (4.60, 42.79)	0.02	P< 0.00001, I^2 =98%	R
Anti-TNF	3	217	15.84 [-7.90, 39.58]	0.19	P< 0.00001, I^2 =99%	R
Conventional	3	228	10.24 (3.32, 17.17)	0.004	P< 0.00001, I^2 =99%	R

Table 2. Main meta-analysis results of the association between treatments and AS patients and controls

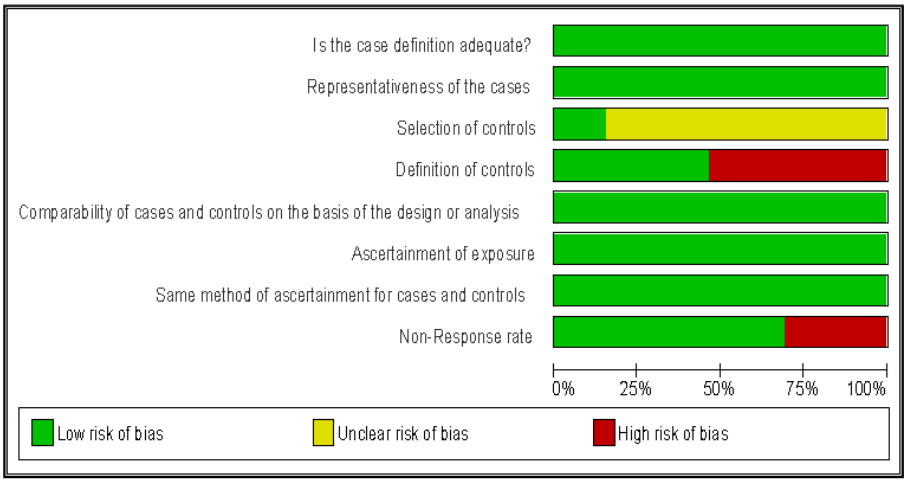

Figure 5. Detailed risk of bias results using the Newcastle-Ottawa Scale for Assessing Quality for observational studies

play a prominent role in AS pathogenesis. The subgroup analysis based on disease activity also demonstrated that serum IL-17 has significant association with elevated BASDAI in AS, demonstrating that IL-17 is correlated with disease activity.

Recent studies have investigated the IL23/IL-17 pathway and its influence on the pathogenesis of AS (GRAVALLESE; SCHETT, 2018; MEI et al., 2011; WENDLING, 2008). IL-17 is secreted by specialized Th17 subset of CD4+ T cells and is involved in host defense mechanisms against pathogens by inducing synthesis and secretion of pro-inflammatory molecules from fibroblasts, endothelial cells, and epithelial cells, including chemokines, antimicrobial peptides and matrix metalloproteinases (IWAKURA; ISHIGAME, 2006; KORN et al., 2007; REYNOLDS; ANGKASEKWINAI; DONG, 2010).

To investigate the contribution of treatment in influencing serum levels of IL-17, subgroup analyses were conducted with untreated patients, with conventional medication and anti-TNF. Our results indicated that mean difference of serum expression of interleukin IL-17 was significantly influenced by the treatment in use, which was highe in untreated patients than controls. Among patients who use conversational therapy, the expression was also significantly higher than controls. No statistical significance was observed for serum expression of anti-TNF-treated patients compared to controls. We also evaluated the influence before and after anti-TNF treatment and the studies do not exhibit any heterogeneity for the impact of the treatments on the outcome, which contributes with the results previously discussed.

Our results were similar to a study performed by Milanez and collaborators (2016), which investigated long-term influence of anti-TNF drugs in IL-23/IL-17 axis at 12 and 24-months of TNF blockade in plasma. They found a strong correlation between IL-23 and IL-17A and ASDAS/PCR after anti-TNF therapy and concluded that the IL-23/IL-17 axis is not influenced by TNF blockade in AS patients despite clinical and inflammation improvements and NSAID intake.

The availability of new biological products targeting the IL-17/IL-23 axis has shown promising results in reducing the rate of radiographic progression in AS (MAGREY, M. N.; KHAN M. A., 2017). IL-17 antagonists secukinumab, ixekizumab, and brodalumab blocking the Th17 pathway by suppressing IL-17 act directly or through inhibition of Th17 cell differentiation (BABAIE, F. et al., 2018). Secukinumab is the first non-TNF alpha inhibitor agent licensed for AS. The studies point towards an efficacious role of IL-17A inhibition strategies targeting AS pathogenesis in a fundamental way with a good safety profile (DUBASH et al., 2019; BLAIR, et al., 2019). New studies involving larger patient groups are needed for the factors affecting serum IL-23/IL-17 levels in patients with AS (DEVECI, 2019).

It is very important to resolve the inconsistencies to increase the credibility of the meta-analysis conclusion. Limitations of the present meta-analysis must be acknowledged. First, evaluating only the cytokine of interest may substitute its contribution to the pathogenesis of the disease. Second, the treatment response or before and after treatment were carried out in a limited number of articles. Finally, many studies do not describe the treatments used by the patients or do not describe the mean concentration of the cytokines. Nevertheless, this is the first meta-analysis that identified the association of serum IL-17 level with AS and disease activity before and during treatment.

CONCLUSION

This meta-analysis reveals that IL-17 is highly expressed in serum of patients with AS, and its amplitude is positively related to disease activity. IL-17 was significantly influenced by the treatment in use; however, the lack of significant difference in the expression of IL-17 in the treatment of patients taking anti-TNF proves that it does not interfere in this pathway. This clinical discovery provides implications for practice and research. Further studies are needed that include case-control trials and large population plus describe the medications that patients were using.

REFERENCES

BABAIE F, HASANKHANI M, MOHAMMADI H, et al. The role of gut microbiota and IL-23/IL-17 pathway in ankylosing spondylitis immunopathogenesis: New insights and updates. **Immunology letters**, v.196, p. 52-62, 2018.

BAETEN D, BARALIAKOS X, BRAUN J, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. **The Lancet.** v. 382, n. 9906, p.1705-1713, 2013.

BLAIR H. A. Secukinumab: A Review in Ankylosing Spondylitis. **Drugs**, v. 79, n. 4, p.433-443, 2019.

BRAUN J, SIEPER J. Ankylosing spondylitis. **The Lancet**, v. 369, n. 9570, p.1379-1390, 2007.

CHEN WS, CHANG YS, LIN KC, et al. Association of serum interleukin-17 and interleukin-23 levels with disease activity in Chinese patients with ankylosing spondylitis. **Journal of the Chinese Medical Association**, v. 75, n. 7, p. 303-308, 2012.

DEVECI H, CAGLIYAN TURK A, OZMEN ZC, DEVECI K. Serum Interleukin-23/17 Levels in Ankylosing Spondylitis Patients Treated with Nonsteroidal Anti-Inflammatory Drugs: A Prospective Cohort Study. **J Interferon Cytokine Res**. v. 39, n. 9, p. 572-576, 2019.

DEVECI H, TURK AC, OZMEN ZC, DEMIR AK, SAY COSKUN SU. Biological and genetic evaluation of IL-23/IL-17 pathway in ankylosing spondylitis patients. **Cent Eur J Immunol**, v. 44, n. 4, p. 433-439, 2019.

DUBASH S, BRIDGEWOOD C, MCGONAGLE D, et al. The advent of IL-17A blockade in ankylosing spondylitis: secukinumab, ixekizumab and beyond. **Expert review of clinical immunology**, 2019.

FATTAHI MJ, AHMADI H, JAFARNEZHAD-ANSARIHA F, et al. Oral administration effects of βd-mannuronic acid (M2000) on Th17 and regulatory T cells in patients with ankylosing spondylitis. **Biomedicine & Pharmacotherapy**, v. 100, p. 495-500, 2018.

GAIDUKOVA IZ, REBROV AP, APARKINA AV, et al. Concentração de interleucina-17a permanece consistentemente alto em pacientes com espondilite anquilosante, recebendo inibidores do fator de necrose tumoral α por um ano. **Arquivo terapêutico**, v. 89, n. 4, p. 80-85, 2018.

GRAVALLESE EM., SCHETT G. Effects of the IL-23–IL-17 pathway on bone in spondyloarthritis. **Nature Reviews Rheumatology**, v. 14, n. 11, p. 631-640, 2018.

HAN GW, ZENG LW, LIANG CX, et al. Serum levels of IL-33 is increased in patients with ankylosing spondylitis. **Clinical rheumatology**, 30.12:1583-1588, 2011.

HREGGVIDSDOTTIR HS, NOORDENBOS T, BAETEN DL. Inflammatory pathways in spondyloarthritis. **Molecular immunology**, v. 57, n. 1, p. 28-37, 2014.

IVANOVA M, MANOLOVA I, GANEVA M, et al. Elevated serum levels of Th17-related cytokines in patients with ankylosing spondylitis. **Journal of the Balkan Tribological Association**, v. 22, n. 3, p. 2244-2257, 2016.

IWAKURA Y, ISHIGAME H. The IL-23/IL-17 axis in inflammation. **The Journal of clinical investigation,** v. 116, n. 5, p. 1218-1222, 2006.

KORN T, OUKKA M, KUCHROO V, et al. Th17 cells: effector T cells with inflammatory properties. **In Seminars in immunology**, v.19, n. 6, p. 362-371, 2007.

LIMÓN-CAMACHO L, VARGAS-ROJAS MI, VÁZQUEZ-MELLADO J, et al. In vivo peripheral blood proinflammatory T cells in patients with ankylosing spondylitis. **The Journal of rheumatology**, v. 39, n. 4, p. 830-835, 2012.

MADEJ M, NOWAK B, ŚWIERKOT J, et al. Cytokine profiles in axial spondyloarthritis. **Reumatologia,** v. 53, n.1, p. 9, 2015.

MAGREY MN, KHAN MA. The paradox of bone formation and bone loss in ankylosing spondylitis: evolving new concepts of bone formation and future trends in management. **Current rheumatology reports**, v. 19, n. 4, p. 17, 2017.

MCGEACHY M J, CHEN Y, TATO CM, et al. The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17–producing effector T helper cells in vivo. **Nature immunology**, v. 10, n. 3, p. 314, 2009.

MCGONAGLE, D. G., MCINNES, I. B., KIRKHAM, B. W., SHERLOCK, J., & MOOTS, R. The role of IL-17A in axial spondyloarthritis and psoriatic arthritis: recent advances and controversies. **Annals of the rheumatic diseases,** v. 78, n. 9, p. 1167-1178, 2019.

MEI Y, PAN F, GAO J, et al. Increased serum IL-17 and IL-23 in the patient with ankylosing spondylitis. **Clinical rheumatology,** v. 30, n. 2, p. 269-273, 2011.

MILANEZ FM, SAAD CG, VIANA VT, et al. IL-23/Th17 axis is not influenced by TNFblocking agents in ankylosing spondylitis patients. **Arthritis research & therapy,** v. 18, n. 1, p. 52-61, 2016.

RABELO CF, BAPTISTA TSA, PETERSEN LE, et al. Serum IL-6 correlates with axial mobility index (Bath Ankylosing Spondylitis Metrology Index) in Brazilian patients with ankylosing spondylitis. **Open access rheumatology research and reviews**, v. 10, n. 21, 2018.

REYNOLDS JM, ANGKASEKWINAI P, DONG C. IL-17 family member cytokines: regulation and function in innate immunity. **Cytokine & growth factor reviews**, v. 21, n. 6, p. 413-423, 2010.

SHERLOCK JP, BUCKLEY CD, CUA DJ. The critical role of interleukin-23 in spondyloarthropathy. **Molecular immunology**, v. 57, n. 1, p. 38-43, 2014.

SOHN DH, JEONG H, ROH JS, et al. Serum CCL11 level is associated with radiographic spinal damage in patients with ankylosing spondylitis. **Rheumatology international,** v. 38, n. 8, p.1455-1464, 2018.

SIEPER, J., PODDUBNYY, D., & MIOSSEC, P. The IL-23–IL-17 pathway as a therapeutic target in axial spondyloarthritis. **Nature Reviews Rheumatology,** v. p. 1-11, 2019.

SMITH JA, COLBERT RA. The interleukin-23/interleukin-17 axis in spondyloarthritis pathogenesis: Th17 and beyond. **Arthritis & rheumatology**, v. 66, n. 2, p. 231-241, 2014.

SMOLEN JS, BRAUN J, DOUGADOS M, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. **Annals of the rheumatic diseases**, v. 73, n. 1, p. 6-16, 2014.

STROUP DF, BERLIN JA, MORTON SC, OLKIN I, WILLIAMSON GD, RENNIE D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. **JAMA,** v. 283, n. 15, p. 2008-2012, 2000.

SVEAAS SH, BERG IJ, PROVAN SA, et al. Circulating levels of inflammatory cytokines and cytokine receptors in patients with ankylosing spondylitis: a cross-sectional comparative study. **Scandinavian journal of rheumatology**, v. 44, n. 2, p. 118-124, 2015.

TAM LS, WEI JCC, AGGARWAL A, et al. 2018 APLAR axial spondyloarthritis treatment recommendations. **International journal of rheumatic diseases,** v. 22, n. 3, p. 340-356, 2019.

TAUROG JD, CHHABRA A, COLBERT RA. Ankylosing spondylitis and axial spondyloarthritis. **New England Journal of Medicine,** v. 374, n. 26, p. 2563-2574, 2016.

YEREMENKO N, PARAMARTA JE, BAETEN D. The interleukin-23/interleukin-17 immune axis as a promising new target in the treatment of spondyloarthritis. **Current opinion in rheumatology,** v. 26, n. 4, p. 361-370, 2014.

VAN DER LINDEN, SJEF; VALKENBURG, HANS A.; CATS, ARNOLD. Evaluation of diagnostic criteria for ankylosing spondylitis. Arthritis & Rheumatism, v. 27, n. 4, p. 361-368, 1984.

VAN DER HEIJDE D, LIE E, KVIEN TK, et al. ASDAS, a highly discriminatory ASAS endorsed disease activity score in patients with ankylosing spondylitis. **Annals of the rheumatic diseases**, v. 68, n. 12, p. 1811-1818, 2009.

WARD MM, ATUL D, ELIE AA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. **Arthritis & Rheumatology**, v. 68, n. 2, p. 282-298, 2016.

WENDLING D, CEDOZ JP, RACADOT, E. Serum levels of MMP-3 and cathepsin K in patients with ankylosing spondylitis: effect of TNFα antagonist therapy. **Joint Bone Spine**, v. 75, n. 5, p. 559-562, 2008.

WENKER KJ, QUINT JM. **Ankylosing Spondylitis**. StatPearls, 2021. Disponível em: <https://www.ncbi.nlm.nih.gov/books/NBK470173/>. Acesso em: 05/11/2021.

ZÚÑIGA LA, JAIN R, HAINES C, et al. Th17 cell development: from the cradle to the grave. **Immunological reviews,** v. 252, n.1, p. 78-88, 2013.