Available online at ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com
Joint Bone Spine 75 (2008) 656–660
JOINT BONE SPINE

Clinical-state-of-the-art

# Pathophysiology of ankylosing spondylitis: What's new?

Thao Pham*

*Service de Rhumatologie, CHU Conception, 147, Boulevard Baille, 13005 Marseille, France*

Accepted 26 September 2008

**Abstract**

Ankylosing spondylitis is a chronic inflammatory joint disease that predominantly affects the sacroiliac joints and spine. Its pathophysiology remains one of the most vexing enigmas of rheumatology. However, new insights have been provided by the recent identification of susceptibility genes other than HLA-B27; evidence of a pivotal role for several proinflammatory cytokines including interleukins 23 and 17; and the recognition that inflammation and structural progression proceed separately from each other.


*Keywords:* Ankylosing spondylitis; Pathophysiology

## 1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease that chiefly affects the sacroiliac joints and the spine. The pathophysiology of AS remains largely unknown. Its association with HLA-B27 was first established in the early 1970s, and AS is one of the best examples of diseases linked to genetic markers. The role of HLA-B27 remains incompletely understood [1]. However, advances made in many fields over the last few years have shed some light on the pathophysiology of AS. The objective of this article is to describe recent data, such as the identification of susceptibility genes other than HLA-B27, the demonstration that proinflammatory cytokines other than TNF are involved in AS, and the dissociation between inflammation and structural progression.

## 2. Ankylosing spondylitis is a polygenic disease

### *2.1. HLA-B27 is a major marker but not the sole marker, for ankylosing spondylitis*

A huge body of evidence establishes that AS is associated with HLA-B27. This association has been found in many populations and ethnic groups, on multiple haplotypes [2]. Some of the HLA-B27 subtypes are not associated with AS, suggesting that subtype polymorphism may modulate the disease [3]. The results of animal studies support these epidemiological findings. Rats transgenic for HLA-B27 and human beta2-microglobulin develop a disease that shares many similarities with human AS. In this model, the disease phenotype can be modulated by manipulating HLA-B27, its peptide repertoire, or its folding [4]. However, although over 90% of patients with AS express HLA-B27, AS develops in less than 5% of HLA-B27-positive individuals, suggesting a role for susceptibility genes outside the major histocompatibility complex (MHC) [5–8]. Twin studies support this possibility: concordance rates are higher in monozygotic twins than in dizygotic twins, indicating a role for genetic factors. Concordance rates for AS are 23% in dizygotic and 63% in monozygotic twins positive for HLA-B27. Similarly, the inherited nature of the disease phenotype (age at onset, activity, and severity) may be only partly dependent on HLA-B27 [9]. In sum, these data suggest that AS may depend on multiple genes [10].

### *2.2. The four best candidate genes for a role in ankylosing spondylitis*

#### *2.2.1. HLA-B27*

The leading candidate is HLA-B27, whose strong link with AS long hindered the detection of other associations in

* Tel.: +33 4 91 38 34 62; fax: +33 4 91 38 38 87.
*E-mail address:* thao.pham@ap-hm.fr

1297-319X/$ - see front matter © 2008 Published by Elsevier Masson SAS.
doi:10.1016/j.jbspin.2008.09.003

familial databases. The latest meta-analysis of linkage studies showed that the most robust and strongest link occurred with the MHC region on the short arm of chromosome 6 [11]. However, links have been found with other regions, most notably on 16q and 10q.

HLA-B27 may contribute about 20–50% of the total genetic risk of AS [10]. New techniques, most notably genome screening, have enabled the identification of susceptibility genes located outside the MHC region [12]. Although many genes outside the MHC region have been investigated, only three likely candidates have been identified: the interleukin-1 (IL-1) gene cluster, ARTS1, and the IL-23 receptor gene (IL-23R) [13].

#### 2.2.2. The IL-1 cluster

The IL-1 cluster contains nine genes on chromosome 2, including the genes for IL-1α, IL-1β, and the IL-1 receptor antagonist (IL-1RN). An association between AS and allelic polymorphisms of the IL-1RN gene was suggested. However, five recent studies found no evidence supporting a role for IL-1RN. In contrast, studies support a role for IL-1a and IL-1b in North America and the United Kingdom, and perhaps in South Korea [14–17]. Although the association linking IL-1 to AS is strong, the magnitude of the genetic risk related to each variant is small, with an attributable risk estimated at 4–6%. IL-1α is a proinflammatory cytokine produced chiefly by activated macrophages. IL-1 overexpression in mice causes severe chronic proliferative arthritis. The role for IL-1 has not been evaluated in animal models of AS and remains unclear in humans [18]. In two therapeutic trials, the IL-1 inhibitor anakinra was effective, suggesting a role for IL-1 in AS. However, the effect was small compared to that of TNF antagonists [19–21]. Extracellular inhibitors seem to have little influence on the effects of IL-1α. Researchers are therefore focusing on the intracellular activity of IL-1 and on its proinflammatory effects.

#### 2.2.3. Aminopeptidase regulator of TNFR1 shedding (ARTS1 or ERAP1)

One of the most exciting discoveries made in recent years is that the ARTS1 gene may contribute as much as 26% of the risk of developing AS [22]. ARTS1 is an endoplasmic reticulum aminopeptidase that has two known effects. One effect is cleavage of cytokine receptors (IL-1, IL-6, and TNF) from the cell surface [23–25]. Loss of function of ARTS1 variants may therefore induce proinflammatory effects. The second effect of ARTS1 is cleavage of the N-terminus of peptide precursors in the reticulum, which ensures that the final peptide length is appropriate for presentation by MHC class I HLA molecules [26,27]. ARTS1 knock-out mice are characterized by decreased expression of surface MHC class I molecules, significantly increased alteration of MHC class I surface markers, and decreased antigen stability with defective antigen presentation at the cell surface [28,29]. As mentioned earlier, the role for HLA-B27 in the pathophysiology of AS remains unclear. Among the many hypotheses put forward to date, one involves presentation of an arthritogenic peptide by HLA-B27. AS does not develop in mice transgenic for HLA-B27 and human β2 microglobulin that are kept in a sterile environment. Nevertheless, this hypothesis has not been fully proven. The role for ARTS1, which tailors peptides for presentation by the MHC, supports the involvement of a group of arthritogenic peptides. These peptides may share a similar shape, rather than an amino acid sequence. Further studies of this possibility are needed.

#### 2.2.4. The interleukin-23 receptor (IL-23R)

Whereas ARTS1 may explain the association between HLA-B27 and AS, the IL-23R gene seems to link the spondyloarthropathies to chronic inflammatory bowel disease and psoriasis. A study reported in late 2006 established that Crohn's disease was associated with the IL-23R gene on chromosome 1p31, a finding that was confirmed in subsequent studies [30,31]. Shortly afterward, an association between IL-23R and psoriasis was demonstrated [32]. Several studies have shown that IL-23R is a major susceptibility gene for AS [22,33,34]. The key role for IL-23 in the pathophysiology of AS will be discussed later on.

In sum, the polygenic nature of AS is firmly established [35]. The identification of new susceptibility genes – IL-1, ARTS1, and IL-23R – has shed light on the pathophysiology of AS, most notably regarding the role for HLA-B27.

## 3. Is ankylosing spondylitis an autoinflammatory disease?

Hypotheses regarding the role for HLA-B27 fall into two main groups. One group ascribes a role to environmental factors, such as arthritogenic peptides and molecular mimicry involving the adaptive and innate immune systems. The other group involves the biochemical characteristics of the HLA-B27 molecule, whose abnormalities may affect cell function. Thus, misfolding of the HLA-B27 molecule or the formation of heavy-chain homodimers has been suggested [36]. The formation of homodimers that are unable to present antigens leads to the build-up of chaperonins such as BIP (immunoglobulin heavy-chain binding protein) and to a stress response related to the endoplasmic reticulum (the unfolded protein response), which in turn induce inflammatory factors such as IL-23.

Thus, HLA-B27 may modulate the inflammatory response to infectious agents, via misfolding with an unfolded protein response and/or via antigen recognition. Therefore, diseases associated with HLA-B27 may be autoinflammatory rather than autoimmune diseases [37], with the entheses being the target in AS.

## 4. The key role for the IL-23/IL-17 axis in ankylosing spondylitis

### 4.1. Cytokines IL-23 and IL-17

IL-23 is a recently identified heterodimeric cytokine that belongs to the IL-12 family. Of the two subunits, p19 and p40, the latter is shared with IL-12. Under the influence of IL-6 and TGFβ, which induce the expression of IL-23R on Th17 cells, IL-23 maintains the orientation of naïve CD4 + T cells to Th17 cells that produce IL-17. IL-17 is a proinflammatory cytokine that induces the production of IL-1, IL-6, TNF, and

proinflammatory chemokines [38,39]. The Th17 line is independent from the Th1 and Th2 lines. IL-23 is produced by antigen-presenting cells including dendritic cells, macrophages, and keratinocytes [40]. IL-23 is an immunoregulating cytokine that links adaptive immunity to innate immunity [41]. IL-23 stimulates the Th17 response to infections (e.g., by extracellular bacteria, protozoans, and fungi) and to the activation of receptors involved in innate immunity such as the toll-like receptor 4 (TLR 4) [42–44].

Several studies have shown a role for the IL-23/IL-17 axis in the pathophysiology of AS. Plasma IL-17 levels are high in patients with AS but not in healthy controls or in patients with rheumatoid arthritis or vitiligo [45,46]. IL-17 levels in joint fluid are higher in reactive arthritis and undifferentiated spondyloarthropathy than in rheumatoid arthritis or osteoarthritis [47]. IL-12–p40 is elevated in patient with spondyloarthropathy or rheumatoid arthritis and decreased in those with osteoarthritis. Given that IL-12–p40 can reflect both IL-12 and IL-23, this result is difficult to interpret. It would be of interest to study IL-12/p70 (IL-12/p35/IL-12/p40) and IL-23 in serum and joint fluid specimens from patients with AS. IL-17 has also been found in joint fluid from children with enthesitis-related arthritis [48].

### *4.2. Is there a link between interferon gamma and IL-17?*

Circulating macrophages and T cells from patients with AS show decreased expression of interferon gamma (IFNγ), independently from their HLA-B27 status [49,50]. Although an IFNγ response exists in patients with spondyloarthropathies, it seems weaker than in other inflammatory autoimmune diseases. When an infection occurs, a weak IFNγ response may lead to increased survival of the microorganism in the body and therefore to a higher risk of reactive arthritis [51]. One of the current hypotheses is that limited IFNγ production during an immune response in a susceptible individual may release the Th17 response, thus acting as a key factor in the pathophysiology of AS [41].

### *4.3. IL-23 as a treatment target*

Recent knowledge on the pathophysiology of AS has led to the development of a new treatment strategy consisting in IL-23 blockade by a human recombinant monoclonal antibody against p40 I-12/23, called ustekinumab or CNTO 1275. In a randomized placebo-controlled trial in patients with Crohn's disease, the response rate was 75% in the ustekinumab arm compared to 25% in the placebo arm, and with the higher dosage half the ustekinumab-treated patients achieved a remission by the end of the study [52]. Furthermore, ustekinumab induced a PASI75 response in 75% of patients with psoriasis [53–55]. In a randomized controlled Phase II trial in patients with psoriatic arthritis, the ACR20, ACR50, and ACR70 response rates after only four weekly injections of ustekinumab were higher (42%, 25%, and 10%, respectively) than in the placebo group (14%,7%, and 0%) [56]. The results suggest that ustekinumab may improve the joint manifestations and skin lesions, with a carry-on effect at week 12, 8 weeks after the last injection. Thus, IL-23 may orchestrate the pathophysiology of three related chronic inflammatory diseases, AS, Crohn's disease, and psoriasis [39].

## 5. Pathophysiology of structural progression in ankylosing spondylitis

Structural progression in AS is slow and irregular, with marked interindividual variations. The modified Stoke AS Spinal Score (mSASSS) is a validated tool for assessing axial structural damage. This score evaluates the anterior sites of the cervical and lumbar vertebras for squaring, erosions, sclerosis, syndesmophytes, and bridging syndesmophytes [57,58]. It can range from 0 (normal) to 72 (bamboo spine). Mean structural progression has been evaluated at 1.5 mSASSS units/2 years, the smallest detectable difference being 2 units/2 years [59]. An increase greater than the smallest detectable difference occurs in only one-third of patients. However, progression is not linear but instead occurs during unpredictable flares [60]. Syndesmophytes are the most common abnormalities and weigh heavily on the mSASSS value, so that the score chiefly measures ossification rather than overall radiological progression [61]. Few factors predicting disease progression have been identified to date. The only predictive factor found consistently in epidemiological studies was the presence of preexisting syndesmophytes [62]. Other factors such as hip involvement and disease duration have been suggested.

The relationship between evidence of inflammation by magnetic resonance imaging (MRI) and the presence of syndesmophytes is complex. The shiny corner sign (Romanus marginal erosions) is associated with an increased risk of having a syndesmophyte 2 years later (odds ratio, 1.5–5.0 depending on the study) [63–65]. Nevertheless, most syndesmophytes develop at sites without MRI evidence of inflammation [65].

Plasma levels of matrix metalloproteinase 3 (MMP3) predicted radiological progression after 2 years in a cohort of 97 patients with AS [66]. Furthermore, MMP3 elevation and a baseline mSASSS greater than 10 units predicted 2-year progression in individual patients [66]. If these results are confirmed by further studies, they may enable early identification of patients at high risk for structural progression. However, no treatments are available for slowing disease progression. TNF antagonists seem to have little or no effect on structural progression within 2–4 years in AS, in contrast to rheumatoid arthritis [67–69].

These data suggest dissociation between inflammation and structural damage, or perhaps a partial link. Inflammation, as assessed clinically, by laboratory tests, or by MRI, is only weakly correlated to structural progression. Structural progression involves the formation of new bone which, from a pathophysiological viewpoint, can be likened to a reparative or stabilizing response to mechanical and inflammatory stress [70]. A recent study of the topography of erosions and new bone formation in Achilles tendon enthesitis suggests that bony spurs may develop slowly, in keeping with our clinical experience, and chiefly after the end of the inflammatory phase [71]. Bone formation is endochondral, intramembranous, and

chondroidal, without cellular hypertrophy or local hypervascularity [72]. These clinico-pathologic data support a role for inflammation as a trigger of an ossification process that becomes partly independent from inflammation.

Rheumatoid arthritis is characterized by an imbalance between bone resorption and bone formation, with excess resorption [73]. Resorption by the osteoclastic cell line is stimulated by the receptor activator of the NF-Kappa B ligand (RANKL), which is activated by TNF, and is associated with a blunted bone-formation response [21]. As a rough approximation, osteoclastic activity can be considered regulated by the RANK/RANKL/osteoprotegerin system and osteoblastic activity by the Dickkopf-1 (DKK-1)/Wnt system. DKK-1 is the naturally occurring inhibitor of bone formation [74]. In rheumatoid arthritis, the inflammatory process mediated by TNF may stimulate bone resorption and inhibit bone formation. Plasma DKK-1 levels are elevated in patients with rheumatoid arthritis and return to normal with TNF antagonist therapy [75]. In AS, in contrast, the imbalance favors bone formation, which is not limited by DKK-1. Plasma DKK-1 levels are extremely low [75]. Bone formation in AS may involve other regulation systems including bone morphogenic proteins and TGFβ [45,76,77].

Many unanswered questions remain regarding the pathophysiology of bone remodeling in AS. The exact role for TNF is unclear. Whether factors other than inflammation and mechanical stress can induce bone formation need to be determined. The long-term effects of TNF antagonists on entheseal inflammation are unknown. A key issue is whether early aggressive treatment can limit the development of inappropriate ossification or repair processes in patients with AS. Notwithstanding these many uncertainties, the pathophysiology of AS is becoming increasingly clear. This improved understanding of AS will lead to clinical and therapeutic improvements.

## References


[1] Brewerton DA, Hart FD, Nicholls A, et al. Ankylosing spondylitis and HL-A 27. Lancet 1973;1:904–7.

[2] Gonzalez-Roces S, Alvarez MV, Gonzalez S, et al. HLA-B27 polymorphism and worldwide susceptibility to ankylosing spondylitis. Tissue Antigens 1997;49:116–23.

[3] Marcilla M, Lopez de Castro JA. Peptides: the cornerstone of HLA-B27 biology and pathogenetic role in spondyloarthritis. Tissue Antigens 2008; 71:495–506.

[4] Tran TM, Dorris ML, Satumtira N, et al. Additional human beta2-microglobulin curbs HLA-B27 misfolding and promotes arthritis and spondylitis without colitis in male HLA-B27-transgenic rats. Arthritis Rheum 2006;54:1317–27.

[5] Saraux A, Guillemin F, Guggenbuhl P, et al. Prevalence of spondyloarthropathies in France: 2001. Ann Rheum Dis 2005;64:1431–5.

[6] Brown MA, Pile KD, Kennedy LG, et al. HLA class I associations of ankylosing spondylitis in the white population in the United Kingdom. Ann Rheum Dis 1996;55:268–70.

[7] Gran JT, Husby G, Hordvik M. Prevalence of ankylosing spondylitis in males and females in a young middle-aged population of Tromso, northern Norway. Ann Rheum Dis 1985;44:359–67.

[8] Reveille JD. Major histocompatibility genes and ankylosing spondylitis. Best Pract Res Clin Rheumatol 2006;20:601–9.

[9] Brown MA. Breakthroughs in genetic studies of ankylosing spondylitis. Rheumatology (Oxford) 2008;47:132–7.

[10] Brown MA, Kennedy LG, MacGregor AJ, et al. Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. Arthritis Rheum 1997;40:1823–8.

[11] Carter KW, Pluzhnikov A, Timms AE, et al. Combined analysis of three whole genome linkage scans for ankylosing spondylitis. Rheumatology (Oxford) 2007;46:763–71.

[12] van der Helm-van Mil AH, Padyukov L, Toes RE, et al. Genome-wide single-nucleotide polymorphism studies in rheumatology: hype or hope? Arthritis Rheum 2008;58:2591–7.

[13] Brionez TF, Reveille JD. The contribution of genes outside the major histocompatibility complex to susceptibility to ankylosing spondylitis. Curr Opin Rheumatol 2008;20:384–91.

[14] Maksymowych WP, Rahman P, Reeve JP, et al. Association of the IL1 gene cluster with susceptibility to ankylosing spondylitis: an analysis of three Canadian populations. Arthritis Rheum 2006;54:974–85.

[15] Sims AM, Timms AE, Bruges-Armas J, et al. Prospective meta-analysis of IL-1 gene complex polymorphisms confirms associations with ankylosing spondylitis. Ann Rheum Dis 2008;67:1305–9.

[16] Kim TH, Stone MA, Rahman P, et al. Interleukin 1 and nuclear factor-kappaB polymorphisms in ankylosing spondylitis in Canada and Korea. J Rheumatol 2005;32:1907–10.

[17] Kim TJ, Kim TH, Lee HJ, et al. Interleukin 1 polymorphisms in patients with ankylosing spondylitis in Korea. J Rheumatol 2008;35:1603–8.

[18] Niki Y, Yamada H, Kikuchi T, et al. Membrane-associated IL-1 contributes to chronic synovitis and cartilage destruction in human IL-1 alpha transgenic mice. J Immunol 2004;172:577–84.

[19] Tan AL, Marzo-Ortega H, O'Connor P, et al. Efficacy of anakinra in active ankylosing spondylitis: a clinical and magnetic resonance imaging study. Ann Rheum Dis 2004;63:1041–5.

[20] Haibel H, Rudwaleit M, Listing J, et al. Open label trial of anakinra in active ankylosing spondylitis over 24 weeks. Ann Rheum Dis 2005;64:296–8.

[21] Wendling D. Interleukin-1: a new therapeutic target for ankylosing spondylitis? Joint Bone Spine 2005;72:357–8.

[22] Burton PR, Clayton DG, et alWellcome Trust Case Control Consortium: Australo-Anglo-American Spondylitis Consortium (TASC). Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nat Genet 2007;39:1329–37.

[23] Cui X, Hawari F, Alsaaty S, et al. Identification of ARTS-1 as a novel TNFR1-binding protein that promotes TNFR1 ectodomain shedding. J Clin Invest 2002;110:515–26.

[24] Cui X, Rouhani FN, Hawari F, et al. An aminopeptidase, ARTS-1, is required for interleukin-6 receptor shedding. J Biol Chem 2003;278:28677–85.

[25] Cui X, Rouhani FN, Hawari F, et al. Shedding of the type II IL-1 decoy receptor requires a multifunctional aminopeptidase, aminopeptidase regulator of TNF receptor type 1 shedding. J Immunol 2003;171:6814–9.

[26] Serwold T, Gonzalez F, Kim J, et al. ERAAP customizes peptides for MHC class I molecules in the endoplasmic reticulum. Nature 2002;419: 480–3.

[27] López de Castro JA. HLA-B27 and the pathogenesis of spondyloarthropathies. Immunol Lett 2007;108:27–33.

[28] Yan J, Parekh VV, Mendez-Fernandez Y, et al. In vivo role of ER-associated peptidase activity in tailoring peptides for presentation by MHC class Ia and class Ib molecules. J Exp Med 2006;203:647–59.

[29] Hammer ND, Schmidt JC, Chapman MR. The curli nucleator protein, CsgB, contains an amyloidogenic domain that directs CsgA polymerization. Proc Natl Acad Sci U S A 2007;104:12494–9.

[30] Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006; 314:1461–3.

[31] Tremelling M, Cummings F, Fisher SA, et al. IL23R variation determines susceptibility but not disease phenotype in inflammatory bowel disease. Gastroenterology 2007;132:1657–64.

[32] Cargill M, Schrodi SJ, Chang M, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet 2007;80:273–90.

[33] Rahman P, Inman RD, Gladman DD, et al. Association of interleukin-23 receptor variants with ankylosing spondylitis. Arthritis Rheum 2008;58: 1020–5.

[34] Rueda B, Orozco G, Raya E, et al. The IL23R Arg381Gln non-synonymous polymorphism confers susceptibility to ankylosing spondylitis. Ann Rheum Dis 2008;67:1451–4.
[35] Breban M, Miceli-Richard C, Zinovieva E, et al. The genetics of spondyloarthropathies. Joint Bone Spine 2006;73:355–62.
[36] Smith JA, Marker-Hermann E, Colbert RA. Pathogenesis of ankylosing spondylitis: current concepts. Best Pract Res Clin Rheumatol 2006;20: 571–91.
[37] McGonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS Med 2006;3:e297.
[38] McGovern D, Powrie F. The IL23 axis plays a key role in the pathogenesis of IBD. Gut 2007;56:1333–6.
[39] Wendling D. Interleukin 23: a key cytokine in chronic inflammatory disease. Joint Bone Spine 2008;75:517–9.
[40] Zheng Y, Danilenko DM, Valdez P, et al. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. Nature 2007;445:648–51.
[41] Layh-Schmitt G, Colbert RA. The interleukin-23/interleukin-17 axis in spondyloarthritis. Curr Opin Rheumatol 2008;20:392–7.
[42] Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, et al. Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. Nat Immunol 2007;8:942–9.
[43] Zheng Y, Valdez PA, Danilenko DM, et al. Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. Nat Med 2008;14:282–9.
[44] Fitch E, Harper E, Skorcheva I, et al. Pathophysiology of psoriasis: recent advances on IL-23 and Th17 cytokines. Curr Rheumatol Rep 2007;9: 461–7.
[45] Wendling D, Cedoz JP, Racadot E, et al. Serum IL-17, BMP-7, and bone turnover markers in patients with ankylosing spondylitis. Joint Bone Spine 2007;74:304–5.
[46] Jandus C, Bioley G, Rivals JP, et al. Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondylarthritides. Arthritis Rheum 2008;58:2307–17.
[47] Singh R, Aggarwal A, Misra R. Th1/Th17 cytokine profiles in patients with reactive arthritis/undifferentiated spondyloarthropathy. J Rheumatol 2007;34:2285–90.
[48] Agarwal S, Misra R, Aggarwal A. Interleukin 17 levels are increased in juvenile idiopathic arthritis synovial fluid and induce synovial fibroblasts to produce proinflammatory cytokines and matrix metalloproteinases. J Rheumatol 2008;35:515–9.
[49] Rudwaleit M, Siegert S, Yin Z, et al. Low T cell production of TNFalpha and IFNgamma in ankylosing spondylitis: its relation to HLA-B27 and influence of the TNF-308 gene polymorphism. Ann Rheum Dis 2001;60: 36–42.
[50] Smith JA, Barnes MD, Hong D, et al. Gene expression analysis of macrophages derived from ankylosing spondylitis patients reveals interferon-gamma dysregulation. Arthritis Rheum 2008;58:1640–9.
[51] Inman RD, Chiu B. Early cytokine profiles in the joint define pathogen clearance and severity of arthritis in Chlamydia-induced arthritis in rats. Arthritis Rheum 2006;54:499–507.
[52] Mannon PJ, Fuss IJ, Mayer L, et al. Anti-interleukin-12 antibody for active Crohn's disease. N Engl J Med 2004;351:2069–79.
[53] Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007; 356:580–92.
[54] Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675–84.
[55] Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665–74.
[56] Gottlieb AB, Menter A, Mendelsohn A, et al. Phase II, randomised, placebo-controlled study of CNTO1275, a human interleukin-12/23 monoclonal antibody, in psoriatic arthritis. Arthritis Rheum 2007;56:4310.
[57] Creemers M, Franssen M, Hof Mv M, et al. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2004.
[58] Wanders AJ, Landewe RB, Spoorenberg A, et al. What is the most appropriate radiologic scoring method for ankylosing spondylitis? A comparison of the available methods based on the Outcome Measures in Rheumatology Clinical Trials filter. Arthritis Rheum 2004;50:2622–32.
[59] Baraliakos X, Listing J, Rudwaleit M, et al. Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. Ann Rheum Dis 2007;66:910–5.
[60] Brophy S, Mackay K, Al-Saidi A, et al. The natural history of ankylosing spondylitis as defined by radiological progression. J Rheumatol 2002;29: 1236–43.
[61] Claudepierre P, Wendling D. Are inflammation and ossification on separate tracks in ankylosing spondylitis? Joint Bone Spine 2008. doi:10.1016/j.jbspin.2008.04.006.
[62] Landewe R, Dougados M, Mielants H, et al. Physical function in ankylosing spondylitis is independently determined by both disease activity and radiographic damage of the spine. Ann Rheum Dis 2008. doi:10.1136/ard.2008.091793.
[63] Baraliakos X, Listing J, Rudwaleit M, et al. Evidence for a link between inflammation and new bone formation in ankylosing spondylitis – a detailed analysis. Ann Rheum Dis 2008;67(Suppl. II):130.
[64] Maksymowych W, Chiowchanwisawakit P, Clare T, et al. Inflammatory lesions of the spine on MRI predict the development of new syndesmophytes in ankylosing spondylitis: evidence for coupling between inflammation and new bone formation. Ann Rheum Dis 2008;67(Suppl. II):130.
[65] van der Heijde D, Landewe R, Baraliakos X, et al. MRI-inflammation of the vertebral unit (VU) only marginally contributes to new syndesmophyte formation in that unit: a multi-level analysis. Ann Rheum Dis 2008;67(Suppl. II):130.
[66] Maksymowych WP, Landewe R, Conner-Spady B, et al. Serum matrix metalloproteinase 3 is an independent predictor of structural damage progression in patients with ankylosing spondylitis. Arthritis Rheum 2007;56:1846–53.
[67] Baraliakos X, Listing J, Brandt J, et al. Radiographic progression in patients with ankylosing spondylitis after 4 yrs of treatment with the anti-TNF-alpha antibody infliximab. Rheumatology (Oxford) 2007;46:1450–3.
[68] van der Heijde D, Landewe R, Einstein S, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum 2008;58:1324–31.
[69] van der Heijde D, Landewe R, Deodar A, et al. Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment not inhibited with infliximab. Ann Rheum Dis 2007;66(Suppl. II):85.
[70] Schett G, Landewe R, van der Heijde D. Tumour necrosis factor blockers and structural remodelling in ankylosing spondylitis: what is reality and what is fiction? Ann Rheum Dis 2007;66:709–11.
[71] McGonagle D, Wakefield RJ, Tan AL, et al. Distinct topography of erosion and new bone formation in Achilles tendon enthesitis: implications for understanding the link between inflammation and bone formation in spondylarthritis. Arthritis Rheum 2008;58:2694–9.
[72] Benjamin M, Toumi H, Suzuki D, et al. Evidence for a distinctive pattern of bone formation in enthesophytes. Ann Rheum Dis 2008. doi:10.1136/ard.2008.091074.
[73] Schett G, Hayer S, Zwerina J, et al. Mechanisms of disease: the link between RANKL and arthritic bone disease. Nat Clin Pract Rheumatol 2005;1:47–54.
[74] Morvan F, Boulukos K, Clement-Lacroix P, et al. Deletion of a single allele of the Dkk1 gene leads to an increase in bone formation and bone mass. J Bone Miner Res 2006;21:934–45.
[75] Diarra D, Stolina M, Polzer K, et al. Dickkopf-1 is a master regulator of joint remodeling. Nat Med 2007;13:156–63.
[76] Lories RJ, Derese I, Luyten FP. Modulation of bone morphogenetic protein signaling inhibits the onset and progression of ankylosing enthesitis. J Clin Invest 2005;115:1571–9.
[77] Francois RJ, Neure L, Sieper J, et al. Immunohistological examination of open sacroiliac biopsies of patients with ankylosing spondylitis: detection of tumour necrosis factor alpha in two patients with early disease and transforming growth factor beta in three more advanced cases. Ann Rheum Dis 2006;65:713–20.