

EDITORIAL

MAIT cells: potent major cellular
players in the IL-17 pathway
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Spondyloarthritis (SpA) refers to a group of chronic inflammatory disorders that share common clinical, biological and pathophysiological characteristics. According to the Assessment of SpondyloArthritis international Society classification criteria, these inflammatory rheumatic diseases are subdivided into axial (Ax) SpA (including both radiographic (r) and non-radiographic (nr) forms) and peripheral SpA. Radiographic AxSpA (rAxSpA) corresponds to ankylosing spondylitis (AS), the prototypic and most common form of the disease. The clinical presentation of SpA is heterogeneous with musculoskeletal features (synovitis, sacroiliitis, spinal inflammation, enthesitis, dactylitis), but also extra-articular manifestations (psoriasis, anterior uveitis and inflammatory bowel diseases (IBDs)). One hallmark of the disease, and especially of AxSpA, is the presence of radiographic changes of the sacroiliac joints (SIJs), but also the development of progressive ossifications at enthesal sites.¹ Although HLA-B27 has been identified as a major genetic marker of susceptibility to the disease, the pathophysiology of SpA still remains imperfectly understood. For roughly 15 years, TNF- α has been known as a leading inflammatory cytokine associated with joint inflammation in SpA. With the development of biological treatments, that is, TNF inhibitors (TNFi), the management of patients with SpA has considerably progressed. However, not all patients primarily respond to these treatments, indicating the involvement of other inflammatory mediators.

In fact, the IL-23/IL-17A axis has been identified as another major contributing pathway to inflammatory reaction in SpA.² Indeed, genome-wide studies performed in patients with AS have identified polymorphisms in the IL-23 receptor (*IL-23R*) as a strong protective genetic factor.³ This polymorphism also

provides protection against IBD and psoriasis through impairment of IL-17A production. The interaction of IL-23 (a heterodimeric cytokine with an IL-12/IL-23 p40 common subunit and a p19 IL-23 specific component) with its receptor leads to activation of signal transducer and activator of transcription 3 (STAT3), which in turn induces the expression of retinoic acid receptor-related orphan receptor- γ t (ROR γ t), a major transcription factor for Th17 cells. Th17 cells are CD4⁺ T-helper cells that produce IL-17 family cytokines, mainly IL-17A and IL-17E, and other inflammatory cytokines, including TNF- α , IL-22 and GM-CSF.⁴ Th17 cells are implicated in chronic inflammation and are considered to drive some autoimmune diseases, such as rheumatoid arthritis (RA), psoriasis, multiple sclerosis (MS), but also SpA.⁵ Indeed, in certain but not all studies, circulating IL-17A has been found to be elevated in AS compared with healthy controls.⁶ The frequency of IL-17A-secreting cells was found to be higher in the spinal facet joints (a site of active inflammation in SpA) of patients with AS compared with samples from patients with osteoarthritis.⁷ Finally, in an experimental model of mouse arthritis, Sherlock *et al* identified a particular T-cell subset infiltrating the entheses.⁸ These cells exhibited a specific CD4⁺CD8⁻CD3⁺ phenotype, and expressed IL-23R and ROR γ t. They responded to IL-23 by producing TNF- α , IL-17A, and also IL-22 and CXCL1. In this model, overexpression of IL-23 by mini-circle technology led to severe inflammatory reaction with enthesitis, synovitis and joint destruction. Of interest, IL-17A was linked to joint inflammation, while IL-22 was linked to osteoproliferative changes.⁸ It should be noted that a similar cellular subset has not yet been identified in humans with SpA.⁹ However, group 3 innate lymphoid cells (ILC3) have been isolated in enthesal tissue



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obtained from individuals without inflammatory disease during spine surgery. These cells expressed ROR γ t, STAT3 and IL-23R and were able to produce IL-17A.¹⁰ Overall, this rationale has led to the development of treatments targeting IL-23 or IL-17A in SpA.² Ustekinumab, a monoclonal antibody targeting the common IL-12/IL-23 p40 subunit, has proven to be effective in psoriasis and psoriatic arthritis (PsA). However, despite encouraging preliminary results in an open-label study, this biological agent is not effective in AS.¹¹ Conversely, two monoclonal antibodies blocking the biological effects of IL-17A are available, namely secukinumab and ixekizumab. The results of phase III clinical trials with these agents confirm the rationale for targeting IL-17A in AS and SpA in general. Both are effective in psoriasis and PsA. Currently, only secukinumab is approved for the treatment of rAxSpA, that is, AS, but not in nrSpA.^{12 13}

Conventional Th17 cells are CD4⁺ helper T cells that are a major source of IL-17A.⁴ However, other cellular subtypes may also produce this inflammatory cytokine, and most of them belong to the innate like-immune system.⁹ Indeed, other cellular sources of IL-17A have been identified. This includes $\gamma\delta$ T cells, KIR3DL2⁺ and KLRG1⁺ T cells, ILC especially ILC3 cells, invariant natural killer T (iNKT) cells, as well as mucosal-associated invariant T (MAIT) cells.^{9 14} The enthesal IL-23R⁺ROR γ t⁺CD4⁺CD8⁻CD3⁺ cells described in the animal model by Sherlock *et al* are also included in this cellular category.⁸ All these immune cell subsets, sensitive to IL-23, are collectively referred to under the term type 17 cells.

MAIT cells belong to the class of innate immune T cells and were first described in 1993 in human blood. The name stems from the abundance of these cells at mucosal and inner barriers, that is, the lamina propria of the gut and liver.^{15 16} This cellular subset is characterised by its dependence on a monomorphic MHC Class I-related protein called MR1 for its selection and activation. MAIT cells express a semi-invariant $\alpha\beta$ TCR. The invariant α -chain is defined by the uniform use of V α 7.2 segment paired with J α 12, 20 or 33 (TCRAVIS2-AJ12, J20 or J33) which associates with a limited number of TCR β chains (figure 1). They are CD8⁺ or double negative (CD4⁻CD8⁻). The other phenotypic markers that characterise MAIT cells include high expression of CD161 (CD161^{high}), expression of receptors for IL-7, IL-12, IL-18 and IL-23, as well as multiple chemokine receptors: CCR6, CXCR6 or CCR5. They also express α 4 β 1, α 4 β 7, CD28, the transcription factor ROR γ t and have an effector memory phenotype (CCR7⁻CD62L⁻CD45RO⁺). MAIT cells are restricted by MR1 molecule.¹⁷ Indeed, MAIT cells are activated by specific microbial non-peptide ligands presented by MR1. The bacterial antigens that may stimulate MAIT cells have been identified as vitamin B₂ (riboflavin)-derived molecules. Thus, MAIT cells play a role as the first line of defense against pathogenic bacteria and yeasts, mainly at mucosal surfaces. On MR1 activation, MAIT cells produce inflammatory

cytokines with a mixed Th1/Th17-like response. Indeed, MAIT cells have the capacity to produce IFN- γ , TNF- α , IL-2, IL-17A and IL-22.¹⁵ MAIT cells are primarily located at mucosal surfaces and in the blood, and they represent around 6% to 10% of circulating CD3⁺ T cells. Due to the expression of chemokine receptors, they can migrate to specific tissues, such as the lung, liver and gut. MAIT cells, as well other innate-like T cells, are at the interface between innate and adaptive immune responses. Their absence in germ-free animals and their role in bacterial defense argue for their involvement in mucosa.¹⁶ Mucosal immunity has been implicated as a contributing factor to the pathophysiology of several systemic immune-mediated diseases. Indeed, MAIT cells are located at the mucosal barrier; they play a role in bacterial defense and may modulate human microbiota; they have the capacity to migrate to the sites of active inflammation and to contribute to local damage. A substantial number of studies have reported the possible involvement of MAIT cells in sterile, non-bacterial inflammatory diseases, including MS, psoriasis, IBD, systemic lupus erythematosus (SLE) and RA.¹⁸ A strong relationship between gut and joint inflammation is well described in SpA.¹⁹ In this way, more than 50% of patients with AS may have subclinical gut inflammation, as evidenced by microscopic signs of inflammation in the colon or ileum. Patients with SpA and chronic gut inflammation have a high degree of SIJ inflammation on MRI,⁹ and around 6.5% of patients with SpA will go on to develop clinical IBD during the course of their disease. Therefore, considering the gut-joint axis in SpA and the role of MAIT cells in mucosal immunity, these innate-like T cells are potential cellular players in SpA.

Five studies have evaluated the frequency of circulating blood MAIT cells, as well as their functional capacity in SpA (table 1).²⁰⁻²⁴ One study also reported results from the synovial compartment.²³ In all these studies, MAIT cells were identified as CD3⁺V α 7.2⁺CD161^{high} cells. In two studies, the patient category that was primary evaluated was not patients with SpA, but rather patients with SLE or fibromyalgia syndrome, respectively, and SpA was used as a comparative group.^{20 21} In these latter studies, there was no difference in the proportion of MAIT cells between patients with SpA and the control group.^{20 21} In the study by Sugimoto *et al*, expression of CXCR4 on MAIT cells was identified as a marker to distinguish SpA from healthy controls (HC).²¹ Hayashi *et al* evaluated 30 patients with AS, among them 50% were receiving a biologic agent. There was a decreased proportion of circulating MAIT cells compared with HC. A correlation was observed between CD69 expression on MAIT cells and disease activity as evaluated by Ankylosing Spondylitis Disease Activity Score (ASDAS).²² In these patients, the levels of IL-17A produced by MAIT cells after activation by phorbol-myristate acetate (PMA)/ionomycin were higher compared with the levels obtained in HC. Finally, Gracey *et al*²³ evaluated a larger group of patients with AS, but 61% of them received a TNFi. According to

Professional APCs: dendritic cells (DC), B cells, Macrophages

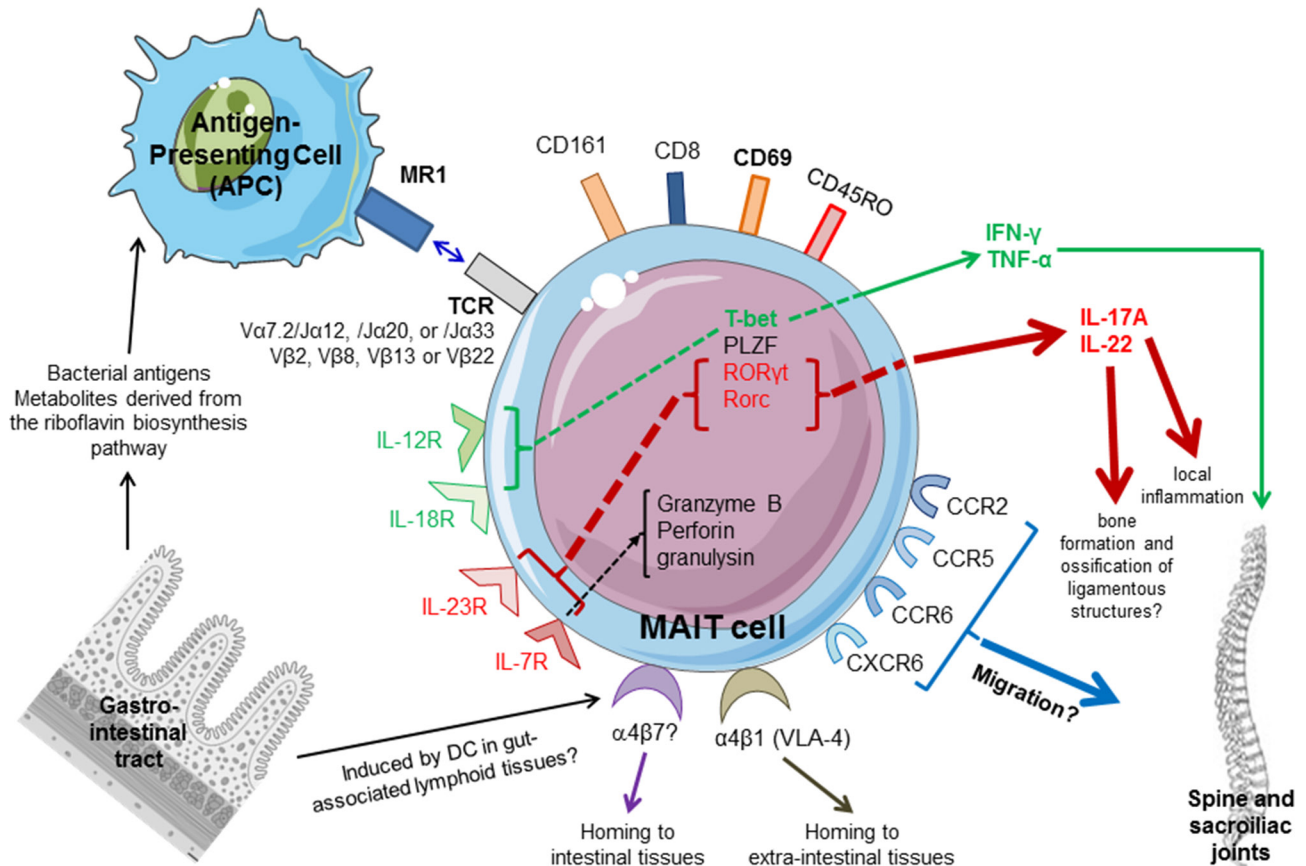


Figure 1 Potential role of MAIT cells in spondyloarthritis (SpA). MAIT cells are activated by MR1 ligands derived from bacteria and yeasts able to produce vitamin B₂ (riboflavin) metabolites. Cytokines, such as IL-7, IL-12, IL-18 and IFN- γ , can also directly activate MAIT cells by an antigen-independent mechanism. MAIT cells are characterised by the semi-invariant T-cell receptor (TCR) composed by an invariant α chain (V α 7.2 segment paired with J α 12, 20 or 33) and a restricted β chain repertoire (V β 2, V β 8, V β 13 or V β 22). They are CD8⁺ or double negative (CD4⁻/CD8⁻), express CD45RO isoform and high levels of CD161, several chemokine receptors (CCR2, CCR5, CCR6, CXCR6,...) and interleukin (IL) receptors, as well transcription factors, including some involved in IL-17A production (IL-23R, ROR γ t/Rorc). MAIT cells are preferentially located at the inner barriers, such as the lamina propria of the intestine. The α 4 integrins (α 4 β 1 and α 4 β 7) regulate tissue homing of activated lymphocytes. MAIT may express α 4 β 7 as a marker suggesting activation in the gut. MAIT express also α 4 β 1 integrin (also known as VLA-4), associated with chemokine receptors responsible for homing to the sites of active inflammation, presumably sacroiliac joints, enthesal structures and peripheral joints in SpA. Once activated by microbial ligands, they can produce high levels of Th17 cytokines, IL-17A and IL-22, and also Th1 cytokines (TNF, IFN- γ). IL-17A promotes local inflammation, while IL-22 contributes to osteoproliferative changes and ligamentous ossifications. Circulating MAIT of patients with SpA express CD69 activation marker. Factors implicated in the type 1 response are in green, while factors involved in the type 17 pathway are in red. PLZF, promyelocytic leukaemia zinc finger; ROR γ t, retinoid-related orphan receptor- γ t.

previous results,²² they observed a low frequency of circulating MAIT cells in AS compared with HC.²³ A subgroup of patients had joint effusion, allowing the assessment of the joint compartment. Indeed, MAIT cells were found in higher proportions in the synovial fluid compared with the circulation.²³ In the blood, MAIT cells had the capacity to produce IL-17A since an elevated frequency of IL-17A⁺ MAIT cells was observed in AS. However, these results were restricted to the male population and were not observed in female patients with AS. Interestingly, the authors demonstrated that MAIT cells were primed by IL-7, a cytokine involved in T cell activation and homeostasis, but not IL-23. MAIT cells may produce IL-17A in response to IL-7.²³ Our group also evaluated circulating

MAIT cells in AS.²⁴ Since MAIT cells may be influenced by different factors including drugs (see below), we chose to include in our study patients without a biological agent or corticosteroids. Indeed, all were treated with non-steroidal anti-inflammatory drugs (NSAIDs). The number of MAIT cells was decreased in the blood of patients with AS compared with HC. We also observed a decreased frequency of $\gamma\delta$ T cells, as well as IFN- γ ⁺CD4⁺ and IFN- γ ⁺CD8⁺ (type 1) T cells. We also evaluated the functional capacity of MAIT cells to express intracellular cytokines (IL-17A, IL-22 and IFN- γ) after stimulation with PMA/ionomycin. Our results showed that patients with AS were characterised by a higher proportion of IL-17A⁺/IFN- γ ⁺ MAIT cells and IL-22⁺ MAIT cells. These results

Table 1 Clinical studies evaluating MAIT cells in ankylosing spondylitis

Author (year) (reference)	Studied population AS (M/F)	Treatments	Control population (M/F)	MAIT cell identification	Main results	Cytokine profile
Cho (2014) ²⁰	21 (19/2)	0% under biologics or CTC	54 SLE (3/51) 66 RA (12/54) 9 Behcet (7/2) 136 HC (69/67)	CD3 ⁺ Vα7.2 ⁺ CD161 ^{high}	▶ No statistical difference in the % or number of circulating MAIT cells between AS and HC	
Sugimoto (2015) ²¹	37 SpA (6/31) (17 AS, 17 uSpA, 1 Psa, 1 ReA)	51% under biologics 48% under CTC	26 FMS (1/25) 21 RA (2/19) 16 HC (2/14)	CD3 ⁺ Vα7.2 ⁺ CD161 ^{high}	▶ No statistical difference in the circulating MAIT cell population among disease groups ▶ Increased expression of CXCR4 on MAIT cells of patients with SpA compared with HC	
Hayashi (2016) ²²	30 (28/2)	50% under biologics 23% under NSAIDs 6% under CTC	21 HC (20/1)	CD3 ⁺ Vα7.2 ⁺ CD161 ^{high}	▶ Decreased proportion of circulating MAIT cells compared with HC ▶ Relationship between CD69 expression on MAIT cells and ASDAS	Higher frequency of IL-17A ⁺ MAIT in the blood of patients with AS compared with HC
Gracey (2016) ²³	54 (36/18)	61% under biologics 58% under NSAIDs	28 HC 16 RA	CD3 ⁺ Vα7.2 ⁺ CD161 ^{high}	▶ Decreased proportion of circulating MAIT cells compared with HC ▶ Increased proportion of MAIT cells in synovial fluid of AS compared with blood compartment	Higher frequency of IL-17A ⁺ MAIT in the blood of male patients with AS compared with HC Lower frequency of IFNα ⁺ MAIT in the blood of AS compared with HC Priming of MAIT cells by IL-7
Toussiroit (2018) ²⁴	36 (27/9)	100% under NSAIDs 0% under biologics or CTC	55 (32/23)	CD3 ⁺ Vα7.2 ⁺ CD161 ^{high}	▶ Decreased number and proportion of circulating MAIT cells in AS compared with HC	Higher number of circulating IL-17A ⁺ IFNα ⁺ MAIT and IL-22 ⁺ MAIT cells in patients with AS compared with HC

AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; CTC, corticosteroids; FMS, fibromyalgia syndrome; HC, healthy controls; M/F, male/female; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis; ReA, reactive arthritis; SLE, systemic lupus erythematosus; uSpA, undifferentiated spondyloarthritis.

were independent of gender. On the contrary, MAIT cells positive for IL-17A and negative for IFN- γ were only increased in female patients with AS. We did not observe a relationship between laboratory parameters of inflammation, disease activity scores (Bath Ankylosing Spondylitis Disease Activity Index or ASDAS), and IL-22⁺ or IL-17A⁺ MAIT cells.²⁴

Overall, these results show that MAIT cells are deregulated in AS and circulate at a low frequency compared with normal subjects. Similar results have been reported in other immune-mediated diseases such as RA, MS, SLE, IBD and psoriasis.¹⁸ MAIT cells have the capacity to migrate to the site of inflammation due to their chemokine receptor expression.¹⁶ As previously reported in RA, MAIT cells in AS are found to be increased in the synovial fluid compared with the blood in patients with peripheral arthritis.²⁵ Whether MAIT cells are also located at the entheses as well as in the SIJ is currently unknown and it is a major limitation of the discussed studies, including ours.²⁴ In fact, such axial skeletal structures are of limited accessibility. In addition, the reduced frequency of MAIT cells in the circulation does not result from apoptosis. This hypothesis was examined in one study, and MAIT cells from patients with AS have comparable caspase-3 and Fas expression as compared with HC.²²

The frequency of MAIT cells was not always reduced in the different studies.^{20,21} This may be related to the patient demographics, but also the treatments they received. The gating strategy that was used in the different studies to analysed MAIT cells by flow cytometry may also explain the heterogeneity of these results. Indeed, several factors may influence MAIT cell frequency and function: they decrease with age, are higher in obese subjects and are reduced with smoking habits.^{15–17} Conversely, gender does not affect MAIT cells.¹⁵ In addition, some drugs or their metabolites may be presented by MRI, and thus may influence MAIT cell function. These include corticosteroids, methotrexate and also NSAIDs (diclofenac).²⁶ The influence of biological agents (TNFi and anti-IL17A agents) on MAIT cells is currently unknown, but it is conceivable that they may modulate their functional capacity. Therefore, this may have biased some results.^{22,23} Alternatively, assessing drug-free patients is challenging and they are difficult to select in clinical practice.

MAIT cells in patients with AS have the capacity to produce IL-17A, but also IFN- γ and IL-22. According to the different studies performed in AS, MAIT cells are characterised by a Th17 or Th1/Th17-like phenotype. MAIT cells express ROR γ t, a transcription factor associated with IL-17A-producing subset.^{15,16} In a mouse model of arthritis, it was demonstrated that MAIT cells became activated on IL-23 stimulation and had arthritogenic potency, suggesting their role in joint inflammation.²⁷ Taken together, these results highlight the potential role of MAIT cells in AS and their capacity to produce IL-17A and contribute to a Th17-like immune response. This also indicates that the source of IL-17A in SpA is not

restricted to conventional CD4⁺ Th17 cells and involves innate-like T cells.⁹

Our results showed the enhanced expression of IL-22 by MAIT cells in AS.²⁴ The role of IL-22 in arthritis has been suggested in a collagen-induced arthritis model, in which IL-22-deficient mice exhibited decreased incidence of arthritis.²⁸ In addition, it has been suggested that IL-22 may promote osteoclastogenesis in RA.²⁹ In SKG mice that developed SpA-like disease after microbial antigen injection, IL-22 together with IL-17A has been shown to promote enthesitis.³⁰ In parallel, in the mouse model of arthritis described by Sherlock *et al*, overexpression of IL-23 induced the production of IL-22 by entheseal IL-23R⁺CD4⁺CD8⁺CD3⁺ T cells, and IL-22 was associated with the induction of genes implicated in the regulation of bone formation, thus promoting ligamentous ossification.⁸ IL-22, together with IFN- γ and TNF- α , also has the capacity to influence the proliferation and differentiation of mesenchymal stroma cell (MSC) towards an osteogenic phenotype. IL-22 alone can promote the expression of osteogenic transcription factors, indicating that these effects on MSC may represent a pathway for new bone formation in AS.³¹ Together with our results,²⁴ this supports the hypothesis that IL-22⁺ MAIT could contribute to bone formation and ossification of ligamentous structures in SpA.

MAIT cells are found at mucosal sites, including the lamina propria of the gut. In IBD, MAIT cells accumulate in the inflamed mucosa of the patients.¹⁸ MAIT cells may express α 4 β 7, an integrin for homing to the intestinal barrier.^{15,16} Similar to AS, IL-17A production by MAIT cells is enhanced in patients with IBD. MAIT cells may also produce IL-17A in the skin of patients with psoriasis.¹⁸ Overall, these data indicate that, in SpA-associated diseases (IBD and psoriasis), MAIT cells are involved in the local inflammatory response. Due to their location, their involvement in bacterial defense, their activation by bacterial riboflavin-derived metabolite antigens and their functional capacity, MAIT cells together with other innate-like T cells may thus contribute to the joint-gut axis that is well described in SpA.³²

However, some unanswered questions remain. The specific expression of chemokines (CCR2, CCR6, CCR9) and α 4 β 1 and α 4 β 7 integrins by MAIT cells has not been determined in AS. This will contribute to a better understanding of the specific homing process to the gut and/or joint of these cells. It will certainly confirm that MAIT cells mainly originate from the gut. Only patients with a radiographic form of the disease (ie, AS) have been evaluated, and results are lacking for the nrAx SpA group. As stated above, the specific effect of biological agents on MAIT cells deserves additional investigation. In fact, it is relevant to examine whether TNFi modulate cytokine production by MAIT cells. Since IL-22 is involved in the regulation of bone ossification,^{29,31} the relationship between IL-22⁺ MAIT cells and SpA radiographic damage (by means of the modified Stoke Ankylosing Spondylitis Spinal Score) is also a relevant question. Finally,

innate-like T cells are not restricted to MAIT cells and include other cellular subsets that have the capacity to produce IL-17A and other cytokines implicated in SpA pathophysiology. For instance, ILC3 cells producing IL-17A and IL-22 are observed in the gut, the circulation and the synovial fluid of patients with SpA.³³ They are also observed in enthesal structures.¹⁰ IL-17A⁺γδ T cells are expanded in the peripheral circulation of patients with active AS.³⁴ In a mouse model of SpA that overexpressed IL-23, γδ T cells accumulated in the entheses, but also the aortic root and the ciliary body.³⁵ The relative contribution of the different innate-like T cells to the Th17 axis in SpA thus warrants further exploration. Finally, one major question is the specific expression of MAIT cells in the entheses of patients with SpA.

Despite these remarks, accumulating data indicate that MAIT cells are involved in AS and SpA in general, contributing to IL-17A production in the circulation, and thus to the IL-17 pathway of SpA. Currently, it is considered that IL-17A production by MAIT cells is 10-fold higher than by conventional Th17 cells.³⁶ MAIT cells are also a source of IL-22 that may participate in the specific pathogenic process of ligamentous ossification of SpA. MAIT cells are deregulated in number, function and location in AS, strengthening the importance of innate and innate-like sources of IL17A and IL-22. All these recent findings pave the way to reconsidering the IL-17 axis in SpA and to examining the contribution of the different innate-like T cells to the inflammatory response in SpA. Whether MAIT cells and/or other innate-like T cells may be a target for future therapeutic intervention (by the use of MR1 ligands) requires additional data on the role of these cells in SpA pathophysiology.

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