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# Immunomodulation with IL-17 and TNF- $\alpha$ in spondyloarthritis: focus on the eye and the central nervous system

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**Abstract:** Tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin-17 (IL-17) are two pro-inflammatory cytokines involved in the pathophysiology of spondyloarthritis (SpA). Therapies targeting TNF- $\alpha$  or IL-17 are used as a second line among SpA patients failing non-steroidal anti-inflammatory drugs. The choice of such treatment has to take into account the patient's comorbidities. Neurologic diseases are common and their association with SpA deserves to be studied. Therefore, the role of TNF- $\alpha$  and IL-17 cytokines is worth investigating in these neuropsychiatric diseases. This review aimed to explore the role of TNF- $\alpha$  and IL-17 in the pathogenesis of uveitis, multiple sclerosis, neuromyelitis optica, Alzheimer's disease, Parkinson's disease and depression. This update is critical to guide the therapeutic management of these co-morbidities in SpA patients.

**Keywords:** Alzheimer's disease, central nervous system, cytokines, depression, IL-17, multiple sclerosis, neuromyelitis optica, Parkinson's disease, spondyloarthritis, tumor necrosis factor alpha, uveitis

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## Introduction

Spondyloarthritis (SpA) is a systemic inflammatory disorder affecting the axial skeleton, peripheral joints and entheses. Extra-articular manifestation such as inflammatory bowel disease, psoriasis and uveitis are often associated. SpA affects 0.1–1% of the general population. Comorbidities are frequent and the most common are represented by osteoporosis, cardiovascular disease, cancer and infections.<sup>1</sup> However, other comorbidities deserve to be investigated, such as neurodegenerative and neuropsychiatric diseases. Indeed, SpA is often diagnosed in young adults, but as life expectancy increases, we are faced with aging patients who may also have neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Moreover, recent evidence indicates that SpA patients face an increased risk of depression (odds ratio 1.8) compared with the general population.<sup>2</sup> The authors also reported a prevalence of depression in nearly 11% of SpA patients and

that up to 1.5% of all SpA patients suffered from dementia, PD, or multiple sclerosis (MS). Psychological distress symptoms contribute to impaired quality of life both directly and indirectly by influencing disease activity.<sup>3–5</sup> These observations led us to take a general interest in pathologies of the central nervous system (CNS), including eye/optic nerve, and more particularly their coexistence with SpA. We therefore decided to focus on certain neurological pathologies due to their frequency in the general population (AD, PD, depression) and/or their potential severity (multiple sclerosis, neuromyelitis optica and uveitis).

Tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin-17 (IL-17) are two pro-inflammatory cytokines involved in the pathophysiology of SpA. Therefore, it is worth investigating their role in neuropsychiatric diseases. It was hypothesized that TNF- $\alpha$  produced by macrophages plays an

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**Table 1.** Comparative efficacy of TNF- $\alpha$  and IL-17 targeted treatments in neuropsychiatric diseases.

	Anti-IL-17	Anti-TNF- $\alpha$
Uveitis	$\pm$	+
Multiple sclerosis	+	-
Neuromyelitis optica	Undefined	-
Alzheimer's disease	Undefined	$\pm$
Parkinson's disease	Undefined	Undefined
Depression	-	-

+, positive action; -, negative action;  $\pm$ , inconclusive action.

important role in neurodevelopment and in the pathophysiology of various neuropsychiatric conditions.<sup>6,7</sup> Actually, TNF- $\alpha$  may activate the hypothalamo-pituitary-adrenocortical axis and serotonergic neuronal transporters, resulting in neuronal destruction or neurotoxic release of glutamate.<sup>8</sup> However, the role of IL-17 remains unclear in these neurologic disorders. In order to optimize the management of SpA patients, it seems necessary to study the role of pro-inflammatory cytokines in the CNS and the impact of treatments used in SpA on these neurological diseases.

In this review, we aimed to explore the role of TNF- $\alpha$  and IL-17 cytokines in the pathogenesis of uveitis, MS, AD, PD and depression and the effect of treatment targeting TNF- $\alpha$  and IL-17 on these neuropsychiatric diseases (Table 1). First, we will focus on the epidemiology of each neurological comorbidity in SpA, then in the pathophysiology mechanisms and targeted treatments. We conducted a selected review in *PubMed* database prior to December 2020 using the following MeSH terms: TNF- $\alpha$ , IL-17, uveitis, Alzheimer's disease, Parkinson's disease, depression, multiple sclerosis, neuromyelitis optica.

## Uveitis

### *Epidemiology of uveitis in SpA*

The estimated prevalence of uveitis in all its types – anterior, intermediate, posterior, or global (panuveitis) – is about 1 per 1000 individuals. The incidence of uveitis is reported between 19 and 88 per 100,000 patients/year.<sup>9</sup> Its impact can be major since its occurrence is complicated by

visual morbidity.<sup>10</sup> SpA is the most common systemic disease associated with uveitis. Studies have concluded that approximately 80% of patients with a history of acute anterior uveitis associated with HLA-B27 gene suffered from SpA family disorders.<sup>11,12</sup> It is worth mentioning that this frequency is about three times lower for HLA-B27 negative patients.<sup>13</sup> Conversely, SpA without HLA-B27 genetic background, particularly in women, has a poorer visual prognosis, probably due to diagnostic delay.<sup>14</sup> Uveitis occurs in 30–50% of ankylosing SpA and predominates in males. Among 902 patients with uveitis recruited by rheumatologists, nearly 50% were recurrent.<sup>15</sup> They reported two independent factors associated with uveitis: HLA-B27 gene and disease duration greater than 10 years. Furthermore, it should be noted that occurrence of uveitis is not related to the activity or severity of the underlying SpA.<sup>16</sup>

### *The role of the IL-17/TNF- $\alpha$ pathway in the pathophysiology of uveitis*

Uveitis is an intraocular inflammatory process, mainly mediated by T-cells.<sup>17</sup> T-cell activation increases the production of pro-inflammatory cytokines such as IL-17 and/or TNF- $\alpha$ . In humans, the presence of IL-17 and TNF- $\alpha$  is increased in the aqueous humor of patients with SpA.<sup>18</sup> Low levels of TNF- $\alpha$  and high levels of IL-17 are found in the serum of patients with uveitis. IL-17 expression was particularly correlated with disease activity.<sup>19</sup> Similarly, the IL-17 serum levels in contrast to TNF- $\alpha$  expression can differentiate non-infectious uveitis from toxoplasmosis or post-viral uveitis.<sup>20</sup> A recent study shows a clear increase in Th17-cells and a significant decrease in regulatory T-cells (Treg-cells) in patients with HLA-B27 positive uveitis.<sup>21</sup>

Animal models of experimental autoimmune uveitis (EAU) provide a better understanding of the pathophysiological mechanisms of uveitis, despite some limitations. Depending on the model of EAU used (genetically modified or requiring the administration of antigenic peptide), Th17 or Th1 immune pathways can be differentially modulated.<sup>22</sup> Some authors have shown an overexpression of TNF- $\alpha$  in EAU.<sup>23</sup> Others reported a predominance of Th17-cells, whose number was correlated with the severity of uveitis.<sup>24</sup> In this outstanding study, it was suggested that Th17-cells may also contribute to uveitis pathogenesis *via* TNF- $\alpha$  induction.<sup>24</sup> In addition, animal studies

have demonstrated the efficacy of antibodies blocking IL-17 or TNF- $\alpha$  to reduce the intensity of uveitis, highlighting their therapeutic value in the disease.<sup>25</sup> However, the strategy of targeting IL-17 may be harmful since it has resulted in retinal photoreceptor toxicity<sup>25</sup> and a “paradoxical” anti-inflammatory effect of the administration of IL-17 in the EAU model was observed in another study.<sup>26</sup>

#### *Uveitis occurrence under anti-IL-17/anti-TNF- $\alpha$ therapy in SpA patients*

SpA patients frequently have recurrent episodes of uveitis.<sup>15</sup> Most of these episodes resolve within 3 months and are usually treated with topical corticosteroids. Monoclonal antibodies targeting TNF- $\alpha$ , in particular adalimumab (ADA) or infliximab, prevent new relapses of uveitis, although some may occur while receiving these treatments.<sup>27</sup> In contrast, the soluble TNF- $\alpha$  trapping receptor (etanercept) is more frequently associated with the emergence of new uveitis than monoclonal antibodies.<sup>28</sup> The incidence rate of uveitis, adjusted for exposure to TNF- $\alpha$  inhibitors (TNFis), in patients with SpA ranges from 2.6 to 3.5 per 100 patients/year.<sup>29–31</sup> A recent analysis of patients included in the Phase III clinical trials of secukinumab (SCK; anti-IL-17 antibodies) revealed a lower incidence of 1.4 per 100 patients/year.<sup>32</sup> However, these studies are not similar, and we cannot conclude that uveitis occurs less frequently with anti-IL-17 therapy *versus* anti-TNF- $\alpha$  therapy.

#### *Efficacy of targeting IL-17 or TNF- $\alpha$ on uveitis*

The availability of different treatment options in the management of uveitis will depend on the severity and its impact on quality of life. In the event of topical steroid and/or local corticosteroid infiltration failures (ineffectiveness or corticosteroid dependence), treatment with monoclonal antibodies targeting TNF- $\alpha$  may be appropriate. Two randomized, double-blind, placebo-controlled trials using ADA *versus* placebo have been conducted in the treatment of non-infectious uveitis (intermediate, posterior, or panuveitis). The VISUAL I study included patients with active uveitis despite 2 weeks of oral corticosteroids.<sup>33</sup> Relapse occurred less frequently in the ADA arm (40 mg every 2 weeks after a loading dose of 80 mg). The VISUAL II study with the same methodology was conducted in patients with a controlled uveitis under oral corticosteroid

therapy between 10 and 35 mg per day.<sup>34</sup> In this study, relapses were significantly less frequent in the ADA group. Therefore, ADA is recommended for patients who have an inadequate response to prior oral corticosteroid therapy, as well as for patients requiring steroid sparing despite immunosuppressive drugs. For treatments targeting IL-17 or IL-23, only SCK has been evaluated in clinical trials. Some authors have reported a successful experience with ustekinumab (blocking the p40 subunit of the IL-12/IL-23 axis) in some patients.<sup>35,36</sup> Currently, several Phase II trials are in progress with this molecule (NCT02648581, NCT03847272, NCT02911116). For SCK, a first study was conducted on individuals with anterior ( $n=4$ ) or posterior ( $n=12$ ) uveitis with encouraging results.<sup>37</sup> Subsequently, three randomized controlled trials (SHIELD, INSURE, ENDURE) evaluating subcutaneous SCK (300 mg every 2 weeks) against placebo failed to demonstrate any advantage regardless of the patient's phenotype (refractory Behcet's uveitis, active non-Behcet's uveitis despite corticosteroids or requiring immunosuppression).<sup>38</sup> More recently, a new study with a small sample of 30 patients suggested that intravenous SCK (10 mg/kg per 2 weeks or 30 mg/kg per 4 weeks) may be better than the subcutaneous formulation.<sup>39</sup> Thus, it is possible that subcutaneous bioavailability may be partly the cause of SCK treatment failure in the randomized studies.

A specific well-conducted study addressing the anterior uveitis typically found in SpA is missing. Several different causes of uveitis are generally grouped together in clinical trials. The heterogeneity in diseases inducing uveitis and anatomical localizations hinders the transfer of results for SpA. Finally, it is worth remembering that MS can rarely be associated with intermediate uveitis.<sup>40</sup> As TNFis may promote demyelinating lesions<sup>41</sup> another therapeutic target will have to be considered.

## **MS**

### *Epidemiology of MS in SpA*

MS is a chronic demyelinating disorder of the CNS. It is an heterogeneous disease, which may be categorized into clinically isolated syndrome, relapsing and/or remitting MS (RRMS), secondary progressive MS and primary progressive MS. The prevalence of MS in SpA patients can be estimated AS from 0.7% to 1.75%.<sup>42</sup> In most

cases reported, SpA preceded the first signs of MS. The interval between the two conditions ranged from 3 to 21 years.<sup>43</sup> One study described four cases of patients who did not previously receive TNFi at the time of MS diagnosis.<sup>44</sup> Most studies conclude that the association of SpA and MS seemed to be a coincidence.<sup>42,45</sup>

#### *The role of the IL-17/TNF- $\alpha$ pathway in the pathophysiology of MS*

MS is a T-cell mediated disease of the CNS (mainly CD8+ cells). In the initial process of RRMS, activated auto aggressive T-cells cross the blood–brain barrier. The activation of T-cells induces recruitment of other inflammatory cells, including macrophages, by secretion of numerous cytokines. So there is an accumulation of macrophages and lymphocytes in the CNS, resulting in demyelination and destruction of axons.<sup>46</sup>

IL-17A is an important player in several autoimmune and inflammatory diseases such as MS and SpA. Several cell types have been described as potential producers of IL-17A, such as astrocytes and oligodendrocytes. Many studies have described the role of IL-17 in MS and all have concluded that there is a clear link between IL-17 expression and disease development.<sup>46–49</sup>

*In vitro* studies and preclinical animal models have shown that IL-17A plays a major role in MS. Numerous studies using experimental models of MS in mice have found a clear association of Th17 and IL-17 with disease severity and progression.<sup>47,48</sup> In humans, IL-17A-producing memory T lymphocytes have been found in brain lesions of MS patients but not in normal samples.<sup>48</sup> In addition, elevated mononuclear cells expressing IL-17A were reported in the cerebrospinal fluid and blood of patients with MS. Two additional studies found increased serum TNF- $\alpha$  and IL-17 levels in MS patients compared with healthy subjects.<sup>50,51</sup>

TNF- $\alpha$  is secreted by innate immune cells such as macrophages, monocytes and differentiated T-cells. In MS, TNF- $\alpha$  levels were found to be increased in active MS lesions and in an animal model of MS. However, it was determined that TNF $\alpha$  plays a dual role in MS. TNF- $\alpha$  and its receptors can either promote neuroinflammation and secondary neuronal damage or exert protective functions under pathological conditions.<sup>46,52</sup>

#### *Efficacy of targeting IL-17 or TNF- $\alpha$ on MS*

TNF- $\alpha$  has two biologically active forms (soluble and transmembrane), as well as two different receptors. TNF- $\alpha$ -receptor 1 (TNFR1) has pro-inflammatory and cytotoxic activity, and the other, TNF- $\alpha$ -receptor 2 (TNFR2), has a rather cytoprotective action. Thus, activation of TNFR2 could improve the differentiation of oligodendrocytes and promote remyelination by inhibiting the pro-inflammatory activity of microglia.<sup>52–55</sup>

This can explain why TNFIs, due to their non-selectivity, could increase disease activity in MS or induce CNS demyelination in SpA patients treated with TNFIs. Moreover, it is believed that in MS an imbalance in favor of pro-inflammatory TNFR1-mediated signaling pathways outweighs beneficial TNFR2-mediated effects. Despite a beneficial effect on monoclonal antibody targeting TNFR1 in experimental autoimmune encephalomyelitis,<sup>56</sup> a TNFR1-Fc, lenercept, induced an increased number of magnetic resonance imaging (MRI) lesions without clinical effect in MS patients.<sup>57</sup> Others theories have also been proposed, such as the impermeability of blood–brain barrier to TNFIs, the dysregulation of TNF- $\alpha$  in patients with RRMS, the alteration of cytokine responses by downregulating interleukin-10 and upregulating interleukin-12 and interferon- $\gamma$  or the fact that TNFIs may unmask an underlying latent infection, which can lead to autoimmune demyelination<sup>54</sup> or aseptic meningitis reflecting CNS inflammation induced by infliximab.<sup>58</sup> Indeed, several case reports have indicated that demyelinating diseases could be a serious adverse event following TNFi treatment<sup>54,59</sup> such as etanercept<sup>60</sup> or ADA.<sup>55</sup> Literature reviews of previously published cases<sup>42,55</sup> identified 20 cases of MS onset upon TNFi therapies.

A randomized controlled study reported interesting results on MS disease activity by IL-17A inhibition.<sup>61</sup> Compared with placebo, SCK significantly reduced the number of cumulative new-gadolinium-enhanced T1 lesions by 67% but non-significantly reduced the number of combined unique active lesions, which was the primary endpoint. No additional adverse events were reported in the SCK arm compared with placebo.<sup>61</sup> Some cases reported the efficacy of SCK in patients with concomitant MS and SpA<sup>62,63</sup> with stability of brain MRI lesions, absence of new relapse and remission of neurological symptoms. Considering these data, IL-17A blockade may become an alternative option for SpA patients with MS.



### *Focus on neuromyelitis optica*

Neuromyelitis optica (NMO) is a severe and relapsing demyelinating disease of the CNS that preferentially affects the spinal cord (myelitis) and the optic nerves (optic neuritis). It was initially recognized as a subtype of MS but it is mainly characterized by the presence of specific serum autoantibodies directed against aquaporin 4.<sup>64</sup>

Several studies indicated that Th17-cells and Th17-cell-cytokines could play an essential role in the pathophysiology of NMO by degrading the blood–brain barrier and promoting the release of autoantibodies. Also suggested is a collaboration between Th17-cells and B-cells inducing CNS damage.<sup>65</sup> A meta-analysis showed that the number of Th17-cells and serum IL-17 levels were higher in patients with NMO compared with healthy subjects.<sup>66</sup>

According to some studies, TNF- $\alpha$  seems to be neuroprotective from inflammatory damage with practically undetectable TNF- $\alpha$  levels in NMO patients.<sup>67</sup> One case of NMO was reported with positive myelin oligodendrocyte glycoprotein antibodies following TNFi for a pustular psoriasis.<sup>68</sup> There were no data concerning IL-17 blockade in NMO.

## **AD**

### *Epidemiology of AD in SpA*

AD is the most common form of dementia in the elderly, resulting in a progressive decline in a number of cognitive functions. At histology level, AD is characterized by age-related aggregation of the amyloid  $\beta$ -protein affecting microglia, astrocytes and neurons. Indirect evidence suggests that initiation is due to strong local inflammatory responses. The prevalence of AD in SpA is unknown but a Korean study found that SpA patients showed a significantly higher prevalence of overall dementia and Alzheimer's dementia. The prevalence was 1.37% for overall dementia and 0.99% for AD in the SpA group<sup>69</sup> while it was 0.87% and 0.63% respectively in the control group.

### *The role of the IL-17/TNF- $\alpha$ pathway in the pathophysiology of AD*

Pro-inflammatory cytokines can be considered as important factors for induction/stimulation of AD and particularly the IL-23/IL-17A pathway.<sup>70</sup> First of all, high serum levels of IL-17A and IL-23

were observed in the AD Chinese patients compared with controls, with higher IL-23 serum level in the female AD patients.<sup>71</sup> Since a high level was observed in human, suppression of IL-23 signaling pathway (*via* inhibition of p40 subunit by local or systemic delivery) reduces AD-like pathology in animal models.<sup>72,73</sup> Thus, it appears that suppression of Th17 development leads to reduced AD-like pathogenesis. Numbers and functions of IL-23-producing monocytes/macrophages were increased in AD patients.<sup>74</sup> IL-23 was able to induce senescence-accelerated mouse prone 8 strain, as an AD animal model.<sup>75</sup> In addition to IL-23, Th17-cells and IL-17A itself were involved in AD pathogenesis. In AD patients, IL-17A was elevated in the cerebrospinal fluid,<sup>76</sup> with an increased activity and differentiation of Th17-cells through ROR $\gamma$  expression.<sup>77</sup> So, the IL-23/17 pathway is involved in AD induction and the development of the first symptoms.<sup>78</sup> However, the late symptoms were not mediated by the IL-23/17 pathway as suggested by the decrease in IL-17 and IL-23 levels reported in established AD patients compared with age- and sex-matched healthy controls.<sup>79,80</sup>

It therefore appears that IL-17A plays an essential role in the initiation and maintenance of AD and its complications during ageing. However, once the disease is established, the influence of IL-17A declines in parallel with the reduction of immune responses.

*Factors explaining high IL-17A expression in AD.* *In vitro*, it was shown that amyloid- $\beta$  protein was able to produce IL-17A after tissular hypoxia.<sup>81</sup> In an AD animal model, gram-negative respiratory infection induced T-cell infiltration and consequently amyloid- $\beta$  deposition, leading to increased glial cell activation and neurodegenerative functions.<sup>82</sup> To explain this association with bacteria, research focused on innate immune response and in particular TLR4. IL-17A was upregulated in an AD transgenic mouse model in a TLR4-dependent manner.<sup>83</sup> TLR4 was involved in recognition of amyloid- $\beta$  and induction of IL-23/17 pathway through NF- $\kappa$ B.<sup>84</sup> Two genetic factors also regulated IL-17A expression in AD. The human leukocyte antigen-DRB1\*1501 alleles play crucial roles in induction of T helper cells (including Th17-cells) against amyloid- $\beta$  protein in human models.<sup>85</sup> In Han Chinese population, the G allele of rs1884444 polymorphism within IL-23 receptor gene was associated with AD.<sup>86</sup>

**Mechanisms involved by IL-17A in AD.** IL-17A is a strong stimulator for neutrophils in the blood.<sup>87,88</sup> In AD animal models, increasing number, functions and recruitment of neutrophils to the inflamed CNS can be a strong mechanism explaining involvement of the IL-23/17 pathway in AD. Expression of FasL on the Th17 and interaction of the molecule with Fas was also reported to induce apoptosis in the neurons in an AD animal model.<sup>89</sup> So, Th17 mediates AD symptoms through induction of neuroinflammation, leading to recruitment and activation of immune cells, such as neutrophils and microglia, which results in damage to neurons.

**TNF- $\alpha$  in AD.** Both microglia and neurons expressed TNF- $\alpha$  at physiological levels, and it appears to be a key pro-inflammatory cytokine upregulated in AD patients with interaction with AD genes.<sup>90,91</sup> Among these genes, a significant association has been found between a polymorphism of exon 6 of TNFR2 and late AD.<sup>91</sup> Furthermore, several TNF- $\alpha$  promoter polymorphisms associated with its increased expression were also associated with inflammatory and infectious diseases. A meta-analysis suggests that TNF- $\alpha$  polymorphism G308A could be associated with an increased risk of AD in China and a decreased risk of AD in Northern European populations.<sup>92</sup> TNF- $\alpha$  is elevated in AD and stimulates the synthesis of amyloid plaques in animal models of AD and in the human brain.<sup>93–95</sup> The high level of TNF- $\alpha$  measured in serum appears to be predictive of the severity of the disease.<sup>96</sup>

#### *Efficacy of targeting IL-17 or TNF- $\alpha$ on AD*

Many indirect effects of various approaches improved AD signs and could be due to IL-17. All-trans-retinoic acid downregulates IL-17A within peripheral blood mononuclear cells of AD patients and was associated with improvement of AD symptoms.<sup>91</sup> Downregulation of IL-17A by injection of transforming growth factor- $\beta$  reduced neuron damage in an animal model of AD.<sup>97</sup> It was highlighted that flavonoid resveratrol downregulated IL-17A and was beneficial on AD symptoms.<sup>98</sup> A vaccine approach with A $\beta$  42 DNA improved AD symptoms through suppression of Th17-cell proliferation and IL-17A secretion.<sup>77</sup> However, no direct systemic evidence of targeting IL-23/17 axis in human is available, mainly due to lack of ability of these antibodies to penetrate the blood–brain barrier.

One review suggested a beneficial effect of TNFi on cognition and behavior based on evidence from animal studies of AD models.<sup>99</sup> There were only three studies in humans and two of them concluded that TNFi are beneficial in AD patients, but studies had a poor level of evidence.<sup>99</sup> Some other results from animal models with TNF receptor knockout suggest an adverse use of TNFi in AD, with worsening extracellular A $\beta$  deposition.<sup>100</sup> Butchart *et al.*<sup>101</sup> found some interesting trends that favored etanercept, but there were no statistically significant changes in cognition, behavior or global function. Overall, TNFi seemed to have a poor efficacy because most antibodies show poor penetration of the blood–brain barrier *via* passive diffusion. Furthermore, it would necessary to obtain a mild to moderate inhibition level in order not to induce adverse events resulting from blocking the physiological roles of TNF- $\alpha$  in the CNS.<sup>94</sup>

## **PD**

### *Epidemiology of PD in SpA*

PD is a neurodegenerative disease characterized by progressive loss of dopaminergic neurons and presence of neuroinflammation. Approximately 2–3% of elderly people are affected by PD. No treatments currently exist to prevent PD and dopaminergic substitution treatments just relieve the consequences of dopaminergic neuron loss. To date, no association between psoriatic arthritis or axial SpA and PD has been identified. However, patients with psoriasis may have on average 38% increased risk to develop PD, possibly as a result of chronic inflammation.<sup>102</sup>

### *The role of the IL-17/TNF- $\alpha$ pathway in the pathophysiology of PD*

PD is characterized by the presence of Lewy bodies that result from an abnormal accumulation of vesicles and aggregated peptides. Alpha-synuclein ( $\alpha$ -syn), a pre-synaptic protein, has been recognized as its main constituent.<sup>103</sup> The presence of self-reactive T-cells directed against  $\alpha$ -syn has recently been identified in Parkinson's patients, suggesting a potential autoimmune origin of the disease.<sup>104</sup> Neuronal death results from T-cells' infiltration into microglia and is promoted by the presence of cytokines and pro-inflammatory chemokines produced by neuronal aggregates.<sup>105</sup>

**IL-17 and PD.** The involvement of Th17 in PD has been confirmed in two studies using mouse models of PD. In the group of mice treated with intraperitoneal injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, an increased proportion of Th17-cells in the substantia nigra and ventral midbrain was observed. Immunization of mice with nitrated  $\alpha$ -syn partially resulted in Th17 polarization of CD4+ T-cells and impaired Treg-cell function.<sup>106,107</sup> Another animal study based on transgenic human rats showed that the presence of the LRRK2 G2019S gene, one of the major mutations of PD-related gene, was not associated with changes in brain Th17-cells but, rather, with decreases in peripheral Th17-cells.<sup>108</sup>

Limited data are available based on clinical studies, and results are heterogeneous according to the technique used. Indeed, patients with PD appear to have a similar level of Th17-cells compared with controls but may contain a higher proportion of cells ready to express IL-17 upon activation.<sup>109</sup> The proportion of IL17-producing cells that can induce an increased Th17/IL-17 activity is unknown. According to Kustrimovic *et al.*,<sup>110</sup> the amount of IL-17 actually secreted by lymphocytes in PD patients is unchanged, whereas it is increased in very few subjects according to Sommer *et al.*<sup>111</sup> Moreover, Kustrimovic *et al.*<sup>110</sup> reported a reduction in the absolute number of Th17-cells per volume of blood in patients with PD, which means that increased presence of IL-17-producing cells is not necessarily correlated with increasing Th17/IL-17-dependent systemic pro-inflammatory effects. Thus, evidence of the involvement of Th17 in PD is limited and controversial.

**TNF- $\alpha$  and PD.** TNF- $\alpha$  expression may contribute to faster dopaminergic neuron degeneration and it was found that a higher genetic pro-inflammatory profile confers a higher risk to develop PD earlier.<sup>112</sup> Some studies have demonstrated abnormally elevated levels of TNF- $\alpha$  in PD patients<sup>113</sup> whereas others found significantly low levels.<sup>114</sup> Kouchaki *et al.*<sup>115</sup> showed that the serum levels of TNF- $\alpha$  and IL-27 may be important prognostic biomarkers of PD with correlation between the serum level of those factors and severity of PD. Moreover, it was shown that TNF- $\alpha$  levels measured in the striatum and cerebrospinal fluid were significantly higher in PD patients than those in controls.<sup>116</sup> One study aimed to determine TNF- $\alpha$  levels in tear samples obtained

from patients with PD and to analyze the relationship between TNF- $\alpha$  values and PD characteristics. They found that tear TNF- $\alpha$  values were significantly higher in patients with PD than in control subjects but without relationship to the duration or severity of PD.<sup>117</sup>

#### *Efficacy of targeting IL-17 or TNF- $\alpha$ on PD*

No case report has been published of Parkinson's syndrome in patients treated with biotherapies (IL-17 or IL-23 inhibitors; TNF- $\alpha$  blockers) in the following indications: psoriasis, psoriatic arthritis and axial SpA. However, in inflammatory bowel disease, Peter *et al.*<sup>118</sup> showed that early exposure to TNFi was associated with substantially reduced PD incidence but further studies are required to determine whether TNFi administered to high-risk PD individuals may mitigate this risk.

## **Depression**

#### *Epidemiology of depression in SpA*

Depression has frequently been reported to be associated with other physical diseases and changes in the cytokine system. In primary care, the average reported prevalence of depression was 12%.<sup>119</sup> In SpA, pooled prevalence of at least moderate depression was 15% using the Hospital Anxiety and Depression Scale threshold of  $\geq 11$ .<sup>120</sup> The prevalence of depression was similar between axial SpA, radiographic SpA and non-radiographic-axial SpA. Patients with depression had significantly higher disease activity.<sup>120</sup> Mood, sleep disorders and pain seem to contribute independently to the poor quality of life in patients with SpA.<sup>121–123</sup>

#### *The role of the IL-17/TNF- $\alpha$ pathway in the pathophysiology of depression*

**IL-17 and depression.** During depression, the role of IL-17 is unclear. In a mouse model, IL-17A has been shown to be involved in depression associated with psoriatic inflammation *via* the NF- $\kappa$ B and p38MAPK pathways, which play a significant role in upregulation of inflammatory mediators in the brain.<sup>124–126</sup> In humans, the presence of higher baseline IL-17 levels appears to be associated with greater symptom reduction in depressed patients treated with association of selective serotonin reuptake inhibitors and bupropion.<sup>127</sup>



**TNF- $\alpha$  and depression.** The association between TNF- $\alpha$  and depression is controversial. Several mechanisms were highlighted to explain how TNF- $\alpha$  may lead to depression or depressive symptoms: the activation of the hypothalamus-pituitary-adrenal axis, the activation of neuronal serotonin transporters and the stimulation of the indoleamine 2,3-dioxygenase, which leads to tryptophan depletion.<sup>128</sup> In a meta-analysis, peripheral TNF- $\alpha$  levels were not significantly increased in the elderly with depression as compared with controls.<sup>129</sup> Another meta-analysis revealed that TNF- $\alpha$  G-308A polymorphism is not associated with susceptibility to depression.<sup>130</sup> Conversely, Himmerich *et al.*<sup>131</sup> found that acutely depressed inpatients had higher levels of sTNF-R p55, sTNF-R p75 and TNF- $\alpha$  than healthy subjects. This is consistent with another meta-analysis which reported significantly higher concentrations of proinflammatory cytokines (TNF- $\alpha$  and IL-6) in depressed subjects compared with control subjects.<sup>132</sup>

#### *Efficacy of targeting IL-17 or TNF- $\alpha$ on depression*

There is no evidence of elevated risk for depression, anxiety or suicide with SCK in a pooled analysis of data from 10 clinical studies in moderate-to-severe plaque psoriasis.<sup>121</sup> However, a case was described of depression exacerbation in a psoriatic arthritis patient possibly induced by SCK.<sup>122</sup> Suicidal ideation was mainly reported with another IL-17 blocker.<sup>123</sup>

On the other hand, one study found that TNFi (infliximab) may be effective in the treatment of depression, anxiety and quality of life in patients with active SpA.<sup>134</sup> It also described some rare cases of suicide in patients treated with TNFi. In one case, a patient treated with adalimumab developed anti-TNF- $\alpha$ -induced lupus and suicidal ideations.<sup>135</sup> However, infliximab was able to reduce signs of depression in the case of systemic inflammation.<sup>136</sup>

The potential missing link between cytokine-induced chronic inflammatory diseases such as SpA and depression could be sleep disorders.<sup>137</sup> Targeting TNF- $\alpha$  and IL-17 decreases pain in SpA; the positive effect of biological disease-modifying anti-rheumatic drugs (bDMARDs) on sleep architecture is barely discriminable from the efficacy of bDMARDs on disease activity. The role of cytokine imbalance on chronic pain and

sleep disorders has been neglected in the field of rheumatology. Imeri and Opp<sup>138</sup> described the regulation of sleep by the immune system in the early 20th. TNF inhibition by etanercept improved sleep patterns as well as sleepiness in two randomized placebo-controlled, double-blind trials involving abstinent alcohol-dependent male adults and patients with obstructive sleep apnea.<sup>139,140</sup> Data studying the impact of targeting IL-17 in sleep disorders in non-rheumatic population are not available.

#### **Fibromyalgia**

Fibromyalgia is a syndrome of unknown etiology characterized by widespread chronic pain very often associated with fatigue, anxiety, depression and sleep disorders. Its prevalence in SpA ranges from 12.5% to 15%<sup>141–143</sup> and 2–7% in the general population.<sup>144</sup> In axial SpA patients, fibromyalgia reaches a prevalence of 25%.<sup>145</sup> Fibromyalgia is likely associated with a CNS sensitization impairment due to stress such as sleep deprivation and chronic pain rather than with cytokine imbalance. As chronic painful stimulations modulate gray matter,<sup>129,130</sup> function, morphology of small nerve fibers<sup>131</sup> and structural plasticity of the brain, fibromyalgia might be considered as a common comorbidity of SpA.<sup>132</sup>

#### *IL-17 and fibromyalgia*

Plasma levels of IL-17A were compared in plasma from 58 fibromyalgia patients and 39 healthy women matched for age and body mass index using the technique of cytometric bead array.<sup>146</sup> IL-17 levels were significantly higher in fibromyalgia patients. The origin of IL-17 amongst IL-17-producing cells was not addressed by this study. A positive but mild correlation between IL-17 and TNF- $\alpha$  plasma concentration ( $r=0.396$ ,  $p=0.003$ ) was found. Otherwise, non-pharmacological intervention such as progressive resistance exercise or relaxation therapy, known to improve fibromyalgia outcome measures,<sup>147,148</sup> do not impact IL-17 levels.<sup>149</sup>

#### **Conclusion**

At the time of personalized medicine, the prescriber should consider patients' comorbidities. According to neuropsychiatric diseases observed in SpA patients, we reviewed arguments to choose the best treatment. In SpA with MS, the best strategy would be to block the IL-17 pathway. In

SpA with severe uveitis, the best strategy would be a monoclonal antibody targeting TNF- $\alpha$ . Even if in some neurological diseases, the exact role of cytokines and the effect of their blockage remains uncertain, it is important to keep in mind that the use of a treatment targeting TNF- $\alpha$  or IL-17 in SpA is likely to interfere with diseases of the CNS (Table 1).

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