

# Psoriasis and uveitis: links and risks

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**Abstract:** Uveitis, an inflammatory disorder of the mid-portion of the eye, is considered a relatively rare but very serious ocular complication of psoriasis. Data on the specific characteristics of uveitis in the background of psoriasis are extremely limited. The presence of uveitis in the context of psoriasis has been estimated to occur in 7–20% of the psoriasis cases. This incidence tends to be higher in patients suffering from psoriasis and psoriatic arthritis (PsA) or PSA alone. Psoriatic uveitis is usually bilateral, chronic, and severe. In term of pathogenesis, both psoriasis and uveitis are considered as paradigms of T-helper 1/T-helper 17 (Th1/Th17) inflammatory reactions. Certain cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), Interleukin-17 (IL-17), IL-23, and IL-6 play a significant role in the pathogenesis of both psoriasis and uveitis. As uveitis shares common pathogenetic mechanisms with psoriasis in certain circumstances, both diseases may benefit from the same targeted biologic therapies. Undiagnosed and under-treated cases of psoriatic uveitis may cause significant morbidity and even vision loss. Larger prospective studies are needed in order to further investigate the association between these two entities.

**Keywords:** psoriasis, uveitis, pathogenetic link

## Introduction

Psoriasis is a chronic, inflammatory, immune-mediated disorder of the skin, affecting 2–3% of the world's population.<sup>1</sup> It has been associated with several comorbidities which include, besides the most common ones (psoriatic arthritis, metabolic syndrome, cardiovascular events, inflammatory bowel disease, and depression), some ophthalmologic conditions.<sup>2</sup> Uveitis, in particular, is being considered as a relatively rare but very serious ocular complication of psoriasis.<sup>3,4</sup>

## Uveitis – definition

Uveitis is described as an inflammation of the tissues that comprise the uveal tract (i.e., iris, ciliary body, and choroid).<sup>5</sup> It can be classified either according to the anatomic parts of uvea that are involved or according to its underlying etiological cause.<sup>5–7</sup> Anterior uveitis involves the iris and/or the ciliary body, intermediate uveitis involves the vitreous humor, while posterior uveitis is characterized by inflammation of the uvea and the choroid.<sup>6</sup> The uveal involvement is, in some cases, unilateral and in others bilateral. The natural course of the disease can be acute, relapsing, or chronic and this is another useful descriptor of the condition.<sup>7</sup> Anterior uveitis, which is four times more common than posterior, is usually accompanied by pain and redness of the eye without vision loss, while intermediate and posterior uveitis are mainly associated with visual symptoms such as floaters or blind spots and may affect central vision.<sup>3,7–9</sup> The prevalence of uveitis

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reaches 100–150 cases/100,000 population in the developed countries and around 2 million people suffer from it worldwide.<sup>9–11</sup> Severe uveitis is considered responsible for 10% of all cases of blindness.<sup>10,12,13</sup> Etiologically, the disease is mainly divided into infectious and non-infectious uveitis. Non-infectious uveitis is the most common form especially in the countries of the developed world (almost 81% of all cases).<sup>15</sup> The majority of non-infectious cases (40%) present in the background of another systematic, autoimmune disease such as ankylosing spondylitis, inflammatory bowel disease, reactive arthritis, sarcoidosis, Behcet's disease, and psoriatic arthritis and psoriasis.<sup>2,3,7,15,16</sup> One-third of the non-infectious uveitis cases are not associated with another systemic disease and they are described as "idiopathic".<sup>3,17</sup> Other possible precipitants of the disease such as trauma, even ocular surgery, or drugs (cidofovir, rifabutin) are identified in a very small proportion.<sup>7,18</sup> Infectious uveitis is much more frequent in tropical and/or developing countries usually in the background of tuberculosis, toxoplasmosis, and onchocerciasis.<sup>14,19,20</sup>

## Psoriasis and uveitis

### Epidemiologic data

The presence of uveitis in the context of psoriasis, as a complication or a comorbidity, has been described for decades and it has been estimated to occur in 7–20% of the psoriasis cases.<sup>21,22</sup> This incidence tends to be higher in patients suffering from psoriasis and psoriatic arthritis (PsA) or PSA alone (1.5–25% of the cases).<sup>23,24</sup> However, there is growing evidence that psoriasis is independently associated with uveitis even in the absence of PsA although there are, still, very few studies in order to confirm this association.<sup>25</sup>

In a cross-sectional study from Singapore, Chandran et al reported that 2 out of 100 psoriasis patients (2%) suffered from uveitis independently associated with the severity of skin disease.<sup>26</sup> In a Turkish case-control study of 100 patients with psoriasis or PsA and 100 controls without ocular complaints, 2 psoriasis patients (2%) were diagnosed with uveitis while none of the controls.<sup>27</sup> Another study found that 9 out of 10 patients with psoriasis without PsA developed uveitis and in the majority of them (7) the diagnosis of psoriasis preceded that of uveitis.<sup>21</sup> A large nationwide Danish study showed that patients with psoriatic skin disease, even in the absence of PsA, are at increased risk for uveitis and that the reverse

relationship (bidirectional relationship) is of clinical importance.<sup>28</sup> A Taiwanese nationwide cohort study which included a large number of patients suffering from psoriasis (n=137,847) or both psoriasis and PsA (n=10,107) and non-psoriatic controls (n=147,954) concluded that patients with severe psoriasis and PsA had the greatest risk of incident uveitis compared with non-psoriatic controls.<sup>29</sup> The group with severe psoriasis without PsA and that with mild psoriasis and PsA had also an increased, but lower, risk of incident uveitis, while in the group of mild psoriasis without PsA not any risk was identified.<sup>29</sup>

The higher prevalence of uveitis in patients with PsA in comparison with those who suffer only from psoriasis was attributed by some authors to the higher frequency of the HLA-B27 seen in patients with PsA. Indeed, in a study by Paiva et al, 67% of the patients with PsA and uveitis were positive for the HLA-B27.<sup>23</sup> Durrani et al compared 36 patients with uveitis and psoriasis with 30 patients with HLA-B27-associated anterior uveitis and 30 patients with idiopathic arthritis and found that 21 of psoriasis patients were negative for the HLA-B27 antigen while 15 of them were positive.<sup>30</sup>

The presence of uveitis as complication of psoriasis treatment has not been extensively described in the literature. Indeed, there are some case series which attribute the presence of psoriatic uveitis to methotrexate or to anti-TNF- $\alpha$  agents as a paradoxical phenomenon due to a possible cytokine imbalance. More data are needed in order to confirm these theories.<sup>31,32</sup>

### Clinical characteristics of psoriatic uveitis

Data on the specific characteristics of uveitis in the background of psoriasis are extremely limited, especially in the dermatologic literature. It has been reported that psoriatic uveitis usually is bilateral, chronic, and severe.<sup>2,3,30</sup> Durrani and Foster found bilateral involvement in 62% of the cases with an average duration of 11.2 weeks, while in a Japanese study, this rate was significantly lower (46%).<sup>30,33</sup> Some authors claim that uveitis related with PsA, especially the axial pattern, may begin as unilateral and become bilateral in the course of the disease.<sup>34,35</sup> The anterior part of the uvea is preferentially involved both in PsA-related uveitis and in psoriasis-related uveitis with its main symptom being the "dry eye".<sup>2,21,22,30,35,36</sup> Posterior uveitis and pan-uveitis, however, are not uncommon in psoriatic uveitis as they have been described in rates reaching 22–44% in several

studies.<sup>3,23,30</sup> Complications of uveitis such as macular edema and retinal vasculitis may occur in the course the disease in patients with psoriasis.<sup>23,30,36</sup> It has been observed that psoriasis patients with uveitis tend to be older compared with uveitis patients in the general population.<sup>25,26,30</sup> Moreover, uveitis usually occurs a long time after the onset of psoriasis.<sup>33</sup> Some authors believe that in the course of the disease psoriasis appears first, followed by uveitis and finally by PsA, thus giving to uveitis the role of potential precursor of PsA.<sup>25,35</sup>

## Uveitis pathogenesis and pathogenetic link with psoriasis

During the last decades, there was a shift in the paradigm of uveitis pathogenesis as was the case with psoriasis.<sup>37–39</sup> Initially, both diseases (i.e., psoriasis and non-infectious uveitis) were thought to represent a T helper-1 (Th-1) driven type of inflammation, but now they are considered as prototypes of both Th1/Th17 inflammatory reactions.<sup>38–40</sup> Th-1 is a subtype of CD4+ cells which is defined by the secretion of interferon-gamma (INF- $\gamma$ ) and is the main cell type that promotes cellular immunity.<sup>41</sup> At some point, it was found that even in an environment with INF- $\gamma$  deficiency, the development of Experimental Autoimmune Uveitis (EAU) was not suppressed leading to the assumption that another subtype of Th cells may also play a crucial role in uveitis pathogenesis.<sup>42</sup> This hypothesis was proved true with the identification of Th-17 cells, another subset of CD4+ cells, which are responsible, mainly, for the production of Interleukin-17 (IL-17) among other cytokines.<sup>43</sup> IL-17 is a pro-inflammatory cytokine involved in several autoimmune diseases such as psoriasis and uveitis.<sup>44</sup> These cells (Th-17) develop from naïve CD4+ cells in the presence of IL-6, transforming growth factor- $\beta$  (TGF- $\beta$ ), and IL-1 $\beta$  and mature and expand in the presence of IL-23.<sup>43</sup> In the absence of IL-23, Th-17 still develops, but their role is not pathogenic, on the contrary, it is homeostatic.<sup>45</sup> Th-17 expresses also other cytokines that have important role in autoimmunity such as IL-22, IL-6, IL-17F, IL-21, INF- $\gamma$ , granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>43</sup> Th-17 cells expressing INF- $\gamma$  have been identified in human uveitis and maybe this is a clue suggesting the overlap and plasticity between Th subtypes, with INF- $\gamma$  showing a regulatory role to uveitis induction by suppressing the Th-17 pro-inflammatory differentiation.<sup>44,46</sup> It has been proposed by some authors that although both Th-1 and Th-17 subsets are activated in autoimmune uveitis,

Th-17 is responsible for the inflammation in the early stages of the disease while Th-1 expression is increased during the late stages and the resolution of the disease.<sup>43,47</sup> This hypothesis has also been stated for psoriasis.<sup>48</sup> Elevated levels of IL-17 have been found in both aqueous humor and serum of people suffering from autoimmune uveitis.<sup>49,50</sup> However, these findings, regarding the human uveitis models, should still be considered with great caution because more data are still needed.

Among other cytokines that play an important role both in psoriasis and uveitis is IL-23 a heterodimeric protein composed of the p19 subunit which is unique to IL-23 and the p40 subunit which is shared with IL-12.<sup>51,52</sup> Increased levels of IL-23 have been found in the serum of patients with active Vogt-Koyanagi-Harada (VKH) and Behcet's uveitis as well as in the vitreous obtained from patients with posterior uveitis compared with control subjects.<sup>53–55</sup> Moreover, single nucleotide polymorphisms (SNPs) in the IL-23R gene have been found to be associated with chronic inflammatory diseases such as psoriasis, uveitis, and others.<sup>51,56,57</sup>

TNF- $\alpha$  is a cytokine that plays a crucial role in the pathogenesis of both psoriasis and uveitis.<sup>44</sup> It has both a membrane-bound form and a soluble form and it can be produced by all immune cells (natural killer cells, activated T-cells, mast cells, endothelial cells) when there is an inflammatory stimulus.<sup>44</sup> TNF- $\alpha$  elevated levels have been identified in the aqueous humor of patients suffering from HLA-B27(+) idiopathic uveitis, VKH, and Behcet's uveitis.<sup>49,58</sup> These levels, however, do not reflect the activity of the disease or the response to the treatment with the anti- TNF- $\alpha$  monoclonal antibody-Adalimumab.<sup>59</sup>

IL-6 plays an important role in the differentiation of naïve CD4+ T cells into Th-17 cells and it is a well-known mediator of autoimmune diseases including uveitis and psoriasis.<sup>49,60</sup> Elevated levels of IL-6 have been found in the aqueous humor of patients with VKH, sarcoid uveitis, Behcet's uveitis, idiopathic, and HLA-B27-mediated uveitis.<sup>49,58</sup> Moreover, it seems that its presence is associated with the occurrence of certain complications of uveitis such as macular edema and vascularization.<sup>49</sup>

Finally, it has been proposed by some authors that the subclinical inflammation in patients with psoriasis result in a breakdown in the barrier between the blood and the aqueous humor thus allowing activated neutrophils from peripheral blood to provoke the attacks of anterior uveitis.<sup>3,26</sup>

## Common therapeutic pathways

The gold-standard treatment of uveitis, in general, includes topical corticosteroids in the form of eye drops, periocular injections, or even intravitreal steroid-releasing implants.<sup>61</sup> However, the growing knowledge of its pathogenesis guided research toward targeted immunomodulating biologic treatments that aim to control active ocular inflammation and relapses without serious systemic or ocular side effects.<sup>62</sup> As uveitis shares common pathogenetic mechanisms with psoriasis, as well as with other immune-mediated diseases, in certain circumstances both diseases may benefit from the same targeted biologic agents.

TNF- $\alpha$  antagonists were initially approved for rheumatoid arthritis and psoriasis and their use in patients who suffered also from uveitis showed evidence of efficacy before they acquired official approval from FDA.<sup>63,64</sup> The first anti-TNF- $\alpha$  agent to be approved for the treatment of non-infectious uveitis was Adalimumab, in 2016, following the VISUAL I & II studies.<sup>65,66</sup> Infliximab, a chimeric monoclonal antibody (mAb) against TNF- $\alpha$  and Golimumab, another human mAb, has been successfully used as an off-label treatment for patients with uveitis.<sup>64,67</sup> On the contrary, Etanercept, a fusion protein of the TNF- $\alpha$  receptor with a human Fc molecule, although approved for psoriasis and other rheumatologic conditions has not demonstrated efficacy in uveitis.<sup>68</sup> In addition, there is a suspicion that it may induce ocular inflammation in certain patients.<sup>69</sup>

Secukinumab is an FDA-approved human antibody against IL-17A, for the treatment of plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis.<sup>39</sup> It has been tested in three phase III dose-dependent studies for the treatment of uveitis (INSURE, ENDURE, SHIELD) but failed to demonstrate efficacy.<sup>70</sup> This was an unexpected event because it was speculated that secukinumab would have been beneficial especially in patients with a higher inflammatory burden as those suffering from posterior uveitis. It was attributed in the subcutaneous route of administration and in the complex role of IL-17 in the pathogenesis of uveitis. Indeed, a study by Letko et al, the intravenous administration of secukinumab showed a higher rate of improvement compared with the subcutaneous.<sup>71</sup> Moreover, the pro-uveitic role of IL-17 in some cases of experimental autoimmune uveitis was not completely clear because it exerted, also, a beneficial role in the course of the disease.<sup>47,70</sup> Finally, one cannot ignore the possibility that secukinumab trials may have failed due to trial design deficiencies.

Ustekinumab, a human mAb against the common subunit p40 of IL-23 and IL-12, is approved for the treatment of plaque psoriasis, active PsA and severe Crohn's disease. It is currently being studied in two phase II trials for the treatment of uveitis STELARA (NCT0291116) and STELABEC (NCT02648581) but the results have not been published yet.<sup>39,51</sup> However, initial case reports have shown encouraging results.<sup>73,74</sup>

## Conclusions

The relationship between psoriasis without PsA and uveitis, although not fully clarified yet, is a fact that should not be ignored by physicians who treat these patients. Periodic ophthalmologic examinations are necessary for psoriasis patients even without symptoms from the eyes. Early diagnosis may lead to suitable treatment choices which will decrease the inflammatory burden of both diseases (i.e., psoriasis and uveitis). Undiagnosed and under-treated cases of psoriatic uveitis may cause significant morbidity and even vision loss. Nevertheless, larger prospective studies are needed in order to further investigate the association between these two entities.

## Disclosure

Professor Elizabeth Lazaridou reports personal fees from Abbvie, personal fees from Novartis, personal fees from Leo, personal fees from Janssen, personal fees from Celgene-Genesys, personal fees from UCB, outside the submitted work. The authors report no other conflicts of interest in this work.

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