Seeing Clearly:

Balancing Perceptions and Facts of Anti-TNFs in SpA and Uveitis

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WORD FROM THE EDITORS:

Uveitis presents in different forms, with acute anterior uveitis (AAU) being the most common extraarticular manifestation associated with spondyloarthropathy (SpA). A variety of studies, with different designs, strengths and limitations, have produced mixed results and have triggered debate in some circles on whether uveitis during anti-TNF therapy is a paradoxical outcome or part of the natural history of the disease itself. Perceptions of a possible differential effect between the soluble receptor etanercept and the anti-TNF antibody therapies (such as adalimumab and infliximab) have emerged. This publication will explore the data published to date, and provide a Canadian clinical context for managing uveitis in patients with SpA on anti-TNF therapy.

CRA SCR

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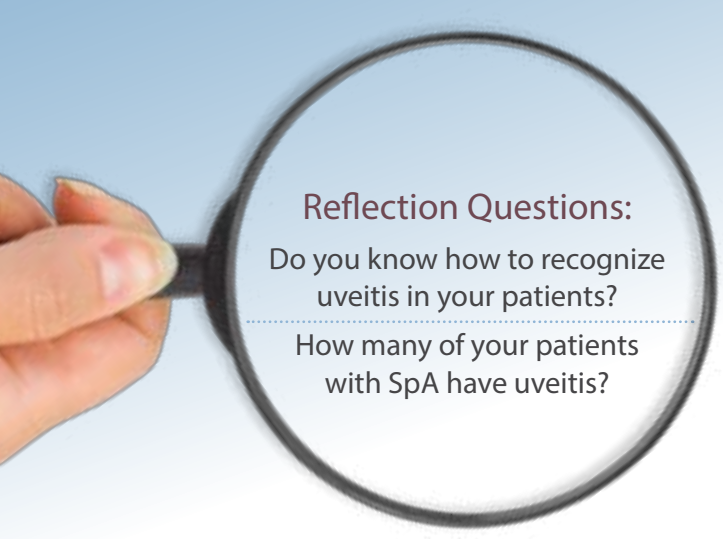
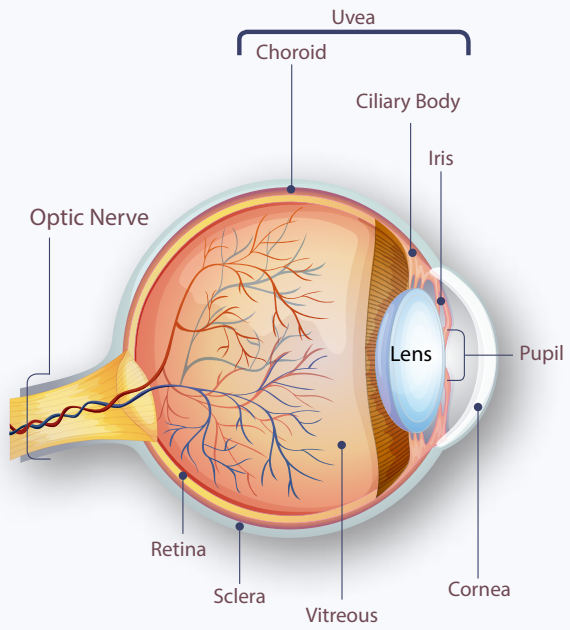


Acute anterior uveitis: the most common extraarticular manifestation of SpA

Uveitis is a family of diseases involving inflammation of parts of the uvea (see Fig. 1).[1] Noninfectious uveitis can be characterized according to the affected region as well as the onset, duration and clinical course (see Tables 1 and 2).[1,2] Its etiology can be idiopathic, related to seronegative SpA, or caused by other systemic inflammatory diseases.[3] Although the incidence of uveitis in the general population is low, reported as 52.4 cases/100 000 person-years,[4] individuals with SpA are at an increased risk of developing acute anterior uveitis.[5,6]

Where possible throughout this paper the type of uveitis is specified, however this article focuses specifically on AAU in SpA. In patients with SpA, 88.7% of uveitis is acute and 90.5% is anterior.[6]

Figure 1. The uvea is the middle part of the eye and is inflamed in uveitis.



Description of Acute Anterior Uveitis in SpA

- Eye pain
- Eye redness
- Photophobia
- Unilateral
- Recurrent
- Alternates between eyes

Table 1. SUN Working Group anatomic classification of uveitis.[2]

Type	Primary site of inflammation	Includes
Anterior uveitis	Anterior chamber	Iritis, iridocyclitis, anterior cyclitis — most common in SpA.
Intermediate uveitis	Vitreous	Pars planitis, posterior cyclitis, hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis, chorioretinitis, retinochoroiditis, retinitis, neuroretinitis
Panuveitis	Anterior chamber, vitreous and retina or choroid	All of the above

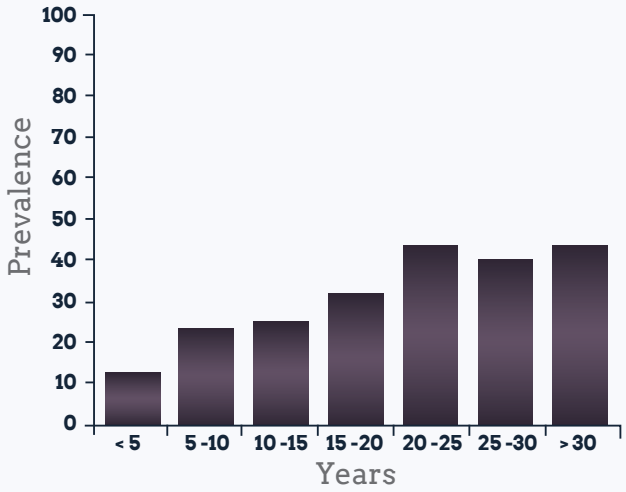
SUN: Standardization in Uveitis Nomenclature.

Table 2. SUN Working Group descriptors of uveitis.[2]

Category	Descriptor	Comment
Onset	Sudden	N/A — most common in SpA.
	Insidious	N/A
Duration	Limited	≤3 months duration
	Persistent	>3 months duration
Course	Acute	Episode characterized by sudden onset and limited duration
	Recurrent	Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration
	Chronic	Persistent uveitis with relapse <3 months after discontinuing treatment

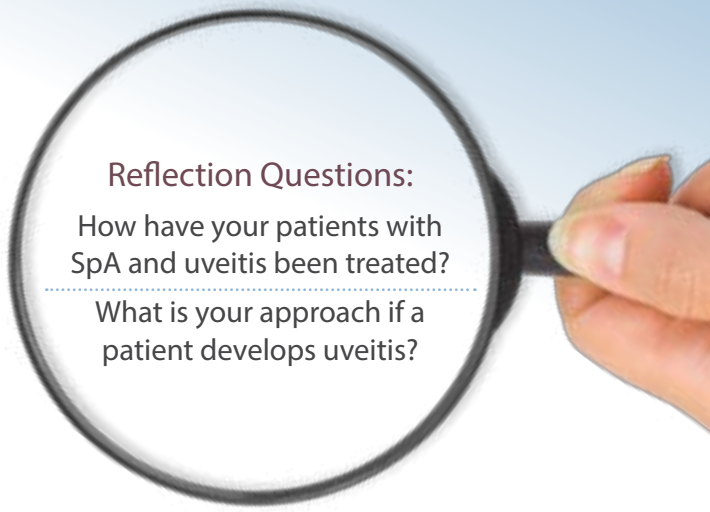
SUN: Standardization in Uveitis Nomenclature.

Figure 2. Prevalence of uveitis in patients with SpA increases over disease duration.[6]



SpA: spondyloarthritis.
Adapted from: Zeboulon et al. Ann Rheum Dis. 2008;67:955-9.

such this analysis may overestimate prevalence). Nevertheless, this study found that regardless of the type of SpA, the prevalence of AAU increases in a nearly linear fashion with disease duration.[6,12,13] Figure 2 shows the prevalence of uveitis in patients with SpA based on disease duration.



Anterior uveitis is restricted to the anterior chamber of the eye, as opposed to intermediate, posterior and panuveitis which are more severe, and uncommonly seen in SpA.[2] Acute uveitis lasts for a maximum of 3 months,[2] with an average of 6 weeks in patients with SpA.[7] Patients with SpA typically develop a unilateral form of uveitis characterized by any combination of eye pain or a bruised feeling, redness and photophobia.[6] Symptoms tend to worsen over a few days. The first episode of uveitis is generally the most severe due to delayed diagnosis. Uveitis in SpA is typically recurrent and alternates between eyes.[8] Approximately half of patients will experience more than one flare.[6] Subsequent flares of uveitis tend to be less severe as patients learn to recognize the early symptoms and seek treatment sooner. The correlation between ankylosing spondylitis (AS) disease activity and the incidence of AAU flares is generally considered to be low.[9]

The development of uveitis can be the first presenting symptom of SpA.[10] Prospective cohort studies have shown that approximately 12-65% of patients with AAU have undiagnosed spondyloarthritis.[5,10,11] In a large prospective case series, although most patients had extraocular disease symptoms before their first attack of uveitis, in 88 out of 136 patients (65%) the rheumatologic diagnosis was made at the time of the uveitis diagnosis.[10] Uveitis has been reported in all types of SpA; however it is most prevalent in AS and psoriatic arthritis (PsA) and least common in undifferentiated SpA. A systematic literature review of 126 articles by Zeboulon et al., which included 29 877 patients with SpA, found a 33.2% prevalence of uveitis in AS, 25.1% in PsA, and 13.2% in undifferentiated SpA.[6] Possible biases in this systematic review may have included: patient participation in more than one study (thus there may be some overlap in the data), and a higher or more severe disease activity in patients participating in clinical trials (as

How is uveitis treated in patients with SpA?

Acute anterior uveitis in patients with SpA is typically managed with a 6 to 8 week course of topical corticosteroid drops administered initially every 30 to 60 minutes while awake, on a tapering schedule.[1] Cycloplegic (dilating) drops, in addition to a nightly corticosteroid ointment, are used to prevent complications.[1] The duration of topical corticosteroids can be modified according to the severity of the flare: more severe uveitis can require treatment extension and in some cases periocular injections and/or systemic oral steroids. Close monitoring is required in order to individualize the tapering schedule for each patient. Uveitis should be quiet before each tapering step. Timely diagnosis of a uveitis flare can lead to a shorter treatment duration and decreased risk of complications.[14]

If a flare is suspected, patients should urgently consult their ophthalmologist or contact their rheumatologist for an emergency referral. If an urgent consultation cannot be scheduled, a visit to the emergency room is recommended. Topical treatment can be effective for most cases of uveitis, regardless of whether or not the patient is receiving an anti-TNF for their SpA.

Approximately 5%[10] to 19%[15] of patients with SpA may develop chronic AAU.[2] Chronic uveitis can reduce quality of life, and lead to complications such as cataracts and temporary visual impairment or, in rare cases, blindness or permanent visual impairment.[14, 15]

The initiation of systemic treatment to manage AAU should be motivated by SpA. For example, anti-TNF therapy would not typically be used as first-line therapy if a patient's arthritic symptoms are in remission with NSAIDs. Moreover, we currently have no reliable

evidence to support a switch from one anti-TNF to another if a patient experiences their first episode of uveitis while on an anti-TNF. However, if a patient with SpA suffers more than one uveitis flare within 3 months of discontinuation of corticosteroid drops, or does not respond to corticosteroid drops while on a particular anti-TNF, then initiation or modification of systemic treatment should be considered.

Can we identify patients with SpA who are at greater risk of developing uveitis?

A positive HLA-B27 status has been shown to increase the prevalence and severity of AAU in patients with SpA.[6] Furthermore, individuals homozygous for HLA-B27 have an increased risk of developing AAU compared to heterozygous patients.[12] Other genetic predispositions for AAU in SpA are currently under investigation.[16]

Geographical variations in prevalence, independent of HLA-B27, have also been observed.[13] A recent study, published in 2015, noted AAU appears to be more common in patients with SpA from North America (35.2%) or Europe (29.3%) compared to Australia (16.2%) or the Middle-East (18.0%).[13] This is likely due to genetic or epigenetic factors outside of HLA-B27.[13]

Do anti-TNF therapies cause uveitis? Why level of evidence matters.

When associations are reported in a particular study, we must ask "Is it real?" Methodological limitations of a study's design can increase the risk of bias, which reduces our confidence in the results. An observed association could be true, or it may be due to chance (e.g., an inadequate sample size) or bias. Bias, which includes confounding, can be introduced through a systematic error in study design, conduct or analysis.[17] For example, studies initially reported that anti-TNFs increased the risk of lymphoma in patients with rheumatoid arthritis (RA);[18, 19] later studies revealed that patients with more severe disease were more likely to be prescribed an anti-TNF, and disease severity (a confounding factor) was the true driver of increased lymphoma risk in these studies.[20, 21]

A Look at the Evidence

Literature Search

To identify relevant publications, excluding reviews, a literature search was perfomed using PUBMED for articles published until February 1, 2016. The following search terms were used:

- "adalimumab", "certolizumab", "etanercept", "golimumab" or "infliximab"
- and "uveitis"
- and "spondyloarthropathy", "spondyloarthritis", "ankylosing spondylitis" or "psoriatic arthritis."

The search was limited to studies published in English which discussed the incidence of uveitis in patients with spondyloarthropathy. This search returned 112 articles. See Fig. 3 for articles that were included after each article was reviewed for relevance.

To understand the quality of the body of evidence on the possible role of anti-TNFs in the development and treatment of uveitis in patients with SpA, each study was assigned a level of evidence. The ranking was based on the 2014 update of the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada (CRA/SPARCC) treatment recommendations for the management of SpA. Level I studies include RCTs and represent the highest level of evidence, whereas Level IV is assigned to expert opinion and represents the lowest level of evidence (see Table 3).[22]

Table 3. Levels of Evidence from the 2014 CRA/SPARCC Guidelines.[22]

Level I:	Metaanalysis, systematic reviews of RCT, or an individual RCT
Level II	Metaanalysis, systematic reviews of observational studies (cohort/case control studies), or individual observational studies, or RCT subgroup/posthoc analysis
Level III	Nonanalytic studies (case reports, case series)
Level IV	Expert opinion

LOE: level of evidence; RCT: randomized controlled trial.
Adapted from: Rohekar S et al. J Rheumatol. 2015;42:666.

The strongest evidence available sits at Level II. The majority of Level II studies found no increased risk of uveitis associated with anti-TNF therapy in patients with SpA (see Fig. 3). Supplementary Table 1 includes information on all Level II studies included.

The strongest evidence available at Level II comes from prospective studies which used a placebo or DMARD control. All of these studies concluded that anti-TNFs (including adalimumab, etanercept, infliximab and certolizumab pegol) either reduce the incidence of uveitis[23-28] in patients with SpA, or do not increase the incidence,[24, 26] compared to the control group.

A divergence in conclusions begins to appear when considering studies that are retrospective and lack appropriate controls and adjustment for confounding.[29-32] The retrospective studies by Lim (2007)[36] and Wendling (2014)[35] reported that etanercept was associated with a higher risk of uveitis than anti-TNF monoclonal antibodies. However, these studies have important limitations, including inadequate control for confounding factors like disease duration and medication exposure (see Supplementary Table 1).

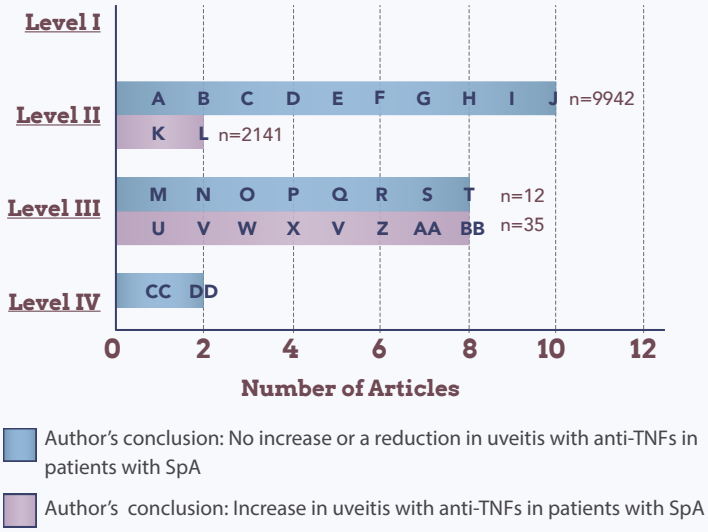
Figure 3. The majority of Level II studies found that anti-TNFs were not associated with an increased risk of uveitis in patients with SpA.[23-34]

Level I:
Not available

Level II:
A-C, 3 Pooled analyses RCTs/OL[23-25]
D, 1 Prospective OS[26]
E, 1 Sub-analysis of prospective OL[27]
F, 1 Prospective OL[28]
G, 1 Post-hoc RCT[29]
H-J, 3 Retrospective OS[30-32]
K, 1 Retrospective claims database OS[35]
L, 1 Retrospective registry-based OS[36]

Level III:
M-BB, 16 Case reports/series[33,34,37-50]

Level IV:
CC-DD, 2 Expert opinions[7,51]



Level II studies are listed in Supplementary Table 1. Level III studies include 16 case reports/series.[24,28,30,32,37-48] RCTs and their pooled analyses were graded at Level II since uveitis was not a primary endpoint in the individual studies. OL: open-label; OS: observational study.

The results become even more mixed moving further down into Level III data (see Fig. 3). The discrepancy between studies highlights the importance of study design and control for bias and confounding when investigating potential drug-related toxicities.

Approximately half of the case reports/series reported that etanercept increased uveitis risk.[34,35,41,42,46,48-50] However, new-onset uveitis has been reported in observational and retrospective studies[27,29-32,35,50] and prospective clinical trials[24] for TNF inhibitors from both classes (soluble receptor and monoclonal antibodies) (see Table 4).

Table 4. Paradoxical reactions observed for anti-TNFs in patients with SpA.

Agent Class	Agent Name	New-onset Uveitis Reported
Monoclonal antibody	Adalimumab[27, 32, 35, 50]	+
	Certolizumab pegol[29]	+
	Infliximab[32, 35, 50]	+
	Golimumab*	?
Soluble receptor	Etanercept[24, 30-32, 35, 50]	+

+: paradoxical reaction described; ?: no data available to date.
* The abstract by Thomas et al. presented at 2015 ACR/ARHP Annual Meeting mentions that iritis was reported in 16% of AS patients taking golimumab, but does not specify if this was new-onset.

For a less common adverse event like uveitis, the length of time the different anti-TNFs have been on the market can impact incidence data. Since etanercept was the first anti-TNF available, this may have contributed to the inconsistency in results between RCTs and observational studies (including registries). This effect is compounded by the fact that the risk of developing uveitis in patients with SpA increases with disease duration.

A current perception is that the soluble receptor TNF inhibitor, etanercept, may be less effective than the monoclonal antibody inhibitors in decreasing recurrences of uveitis in patients with SpA. In fact, the recent ACR/SAA/SPARTAN (American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network) guidelines,[52] which are discussed in the next section, include a conditional recommendation to this effect. However, results from pooled analyses of RCTs are mixed.

A commonly cited meta-analysis by Braun and colleagues (the only RCT-based study used to support the ACR recommendation) reported a trend in different efficacies for uveitis, and not a statistically significant difference, between infliximab and etanercept[23] (see Supplementary Table 1). In contrast, the recent pooled analysis by Wu and colleagues, which has the largest number of patients of the three pooled analyses, found that etanercept was more effective than placebo in reducing the incidence of uveitis, while the monoclonal antibodies (certolizumab pegol or infliximab) did not differ significantly from placebo[25] (see Fig. 4). This pooled analysis included only RCTs (≥12 weeks) with a parallel or crossover design of TNF inhibitor versus placebo. Methodological quality and risk of bias was assessed by two independent reviewers and further assessed using the modified

Jadad criteria (an 8-item scale to assess quality). Results from the Wu et al. pooled analysis are not supported by other studies and, at this point, there isn't a high enough level of consistent evidence to draw reliable conclusions concerning the possible differential efficacy of anti-TNF agents in the treatment of uveitis in patients with SpA. While the efficacy of etanercept in treating uveitis remains unclear, these studies add to the body of evidence demonstrating etanercept does not cause uveitis.

Should the ability to treat uveitis be considered when choosing an anti-TNF therapy?

None of the five anti-TNFs available to treat SpA are currently approved for uveitis treatment or prophylaxis in Canada.[53-57] However, based on the results available, guideline committees have tried to provide guidance to physicians treating patients with SpA and frequently recurrent or chronic uveitis.

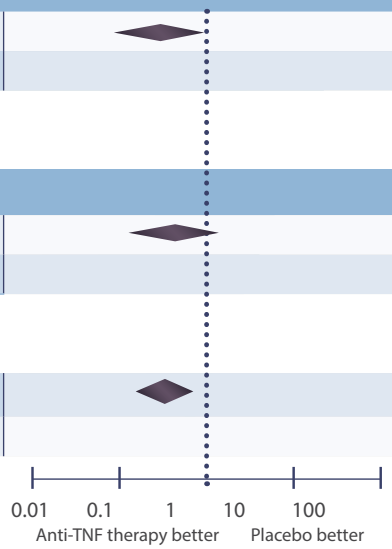
In the absence of a history of uveitis, the selection of appropriate therapy should depend on the patient's SpA features and level of disease activity.[22]

When anti-TNF therapy is indicated for patients with SpA with a personal or severe family history of uveitis, agent choice is less clear. The CRA/SPARCC guidelines recommend selecting an anti-TNF agent which can treat both SpA and its extraarticular manifestations.[22] The committee acknowledges anti-TNF treatment of uveitis may affect drug choice, but provide no additional recommendation.

The 2015 Guidelines for AS and non-radiographic axial SpA published by the ACR/SAA/SPARTAN provide the following guidance: in adults with AS and frequently recurrent iritis episodes (a type of anterior uveitis[2]), infliximab or adalimumab is conditionally recommended over etanercept to decrease the recurrences of iritis (see Table 5).[2,52] This recommendation was based on three retrospective observational studies[26,30,31] and the Braun pooled analysis[23] discussed above.[52] The

Figure 4. Meta-analysis of six RCTs investigating uveitis in AS patients who received an anti-TNF or placebo. [25]

Study or Subgroup	Anti-TNF therapy Events	Anti-TNF therapy Total	Placebo Events	Placebo Total	Odds Ratio Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 receptor fusion proteins						
Subtotal (95% CI)		457		206	61.0%	0.30 [0.09, 0.94]
Total events	3		10			
Heterogeneity: Chi² = 1.15. df=2 (P = 0.56); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						
1.1.2 monoclonal antibodies						
Subtotal (95% CI)		280		156	39.0%	0.43 [0.12, 1.49]
Total events	4		6			
Heterogeneity: Chi² = 0.77, df = 2 (P = O.68); I² = 0%						
Test for overall effect: Z = 1.34 (P = 0.18)						
Total (95% CI)		737		362	100.0%	0.35 [0.15, 0.81]
Total events	7		16			
Heterogeneity: Chi² = 2.10, df = 5 (P = 0.83); I² = 0%						
Test for overall effect: Z = 2.46 (P = 0.01)						
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%						



*Recommendation based on very low-quality evidence, with no evidence of increased harms;[52] †Recommendation based on good-quality evidence;[7] As a corticosteroid-sparing regimen in seronegative SpA.[7]
Adapted from: Wu et al. BMC Musculoskelet Disord. 2015;16:19.

panel acknowledges this recommendation is based on very low-quality evidence, along with no evidence of increased harms.

A committee of the American Uveitis Society recommended consideration of infliximab and adalimumab as corticosteroid-sparing treatment for patients with chronic SpA-related uveitis or in severe, vision-threatening or debilitating uveitis requiring systemic immunomodulatory therapy or as adjunctive treatment to corticosteroid treatment in acute SpA-related uveitis (see Table 5).[7] Most uveitis related to SpA is managed with a 6-8 week course of corticosteroid drops.[1]

Table 5. Anti-TNF strategy to consider for patients with SpA, in the context of uveitis history (when an anti-TNF is indicated for articular manifestations).

History of Uveitis	Anti-TNF Management Strategy to Consider
No history	Anti-TNF choice is based on managing a patient's current SpA features and level of disease activity[22]
Frequently recurrent uveitis (repeated flares separated by at least 3 months of disease inactivity without treatment)	Consider adalimumab or infliximab over etanercept[52]*
Chronic uveitis (persistent uveitis with relapse occurring less than 3 months after treatment discontinuation)	Consider adalimumab or infliximab[7†‖]

*Recommendation based on very low-quality evidence, with no evidence of increased harms;[52] †Recommendation based on good-quality evidence;[7] As a corticosteroid-sparing regimen in seronegative SpA.[7]

Case Snapshot #1

Female patient with axial SpA

- 32 years old
- Receiving anti-TNF therapy, arthritic symptoms are in remission
- Complains of steadily worsening eye pain and redness, with some sensitivity to light

Would you consider changing this patient's systemic treatment? Systemic therapy should only be modified if the uveitis becomes chronic or does not respond to standard treatment.

Case Snapshot #2

Male patient with axial SpA

- 29 years old
- Has symptomatic disease, with a BASDAI score >4
- Previously failed 2 NSAIDs

Scenario A: The patient has no history of uveitis.

Scenario B: The patient has experienced recurrent, alternating uveitis over the past 5 years, with increasing frequency in the last year. The patient is having difficulty discontinuing corticosteroid drops because a flare occurs within 2-3 weeks of stopping treatment.

For each of these scenarios, what factors do you consider when selecting an anti-TNF in this biologic-naïve patient with SpA?

Scenario A: The choice of anti-TNF depends on the patient's SpA features and level of disease activity. There is currently no indication for uveitis prophylaxis with anti-TNFs in Canada.

Scenario B: Consider the patient's history of uveitis when selecting an anti-TNF. The patient is experiencing chronic uveitis and meets the criteria for treating axial SpA with an anti-TNF. Current guidelines (ACR/SAA/SPARTAN, American Uveitis Society) recommend adalimumab or infliximab. Rheumatologists and ophthalmologists should work together to choose an appropriate anti-TNF to treat all manifestations of the patient's disease.

Key Points

- Patients with SpA should be counselled on the risk factors for uveitis (disease duration, HLA-B27 status) and the early symptoms of a flare.
- The correlation between AS disease activity and the incidence of acute anterior uveitis is generally considered to be low.
- Most uveitis cases are managed with a short course of topical corticosteroid drops.
- The highest quality evidence available indicates that anti-TNFs, including etanercept, do not cause uveitis.
- Active collaboration between rheumatologists and ophthalmologists is key for developing an optimal treatment plan to effectively manage both joint and ocular manifestations.

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