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ORIGINAL ARTICLE

Anti-TNFα agents and methotrexate in spondyloarthritis related uveitis in a Chinese population

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Abstract This study seeks to evaluate the clinical characteristics of spondyloarthritis (SpA)-related uveitis in a cohort from South China and to assess the efficacy and safety of therapies based on TNF blockers. SpA patients with uveitis admitted to a south China hospital were enrolled. Demographic information, clinical characteristics, laboratory findings, intraocular inflammation, visual acuity, macular thickness, and treatments were documented. Of the 1,036 SpA patients reviewed, 182 had uveitis. Ankylosing spondylitis (AS) was the most common subtype. Unilateral uveitis was found in 51 cases (51/182, 28.0 %), and unilateral alternating uveitis was found in 75 cases (75/182, 41.2 %). Half of the cases were recurrent uveitis (52.2 %), and acute onset was common (76.4 %). The most serious complication was vision loss (0.5 %). No significant difference in disease activity was found between the SpA patients with or without uveitis. Predominant improvements were found in cases treated with all three anti-TNFs (infliximab, adalimumab, and etanercept) and anti-TNFs plus methotrexate (MTX). Monotherapy of methotrexate was not adequate for inducing remission. Monotherapy of etanercept was not as effective as adalimumab and infliximab, mainly in the prevention of recurrence. No significant difference in effectiveness was found among the three anti-TNFs if MTX was added. Etanercept plus MTX were well tolerated. Infliximab and adalimumab were associated with more tuberculosis and/or hepatitis flares. Uveitis is common in SpA patients. Severe complications may develop in prolonged and intractable cases. Treatments based on anti-TNFs had good clinical response, and better safety documentation were observed in etanercept plus MTX compared to the other two anti-TNF monoclonal antibodies plus MTX.

Keywords Spondyloarthritis · Uveitis · TNF blockers · Methotrexate

Introduction

Uveitis is an ocular inflammatory condition involving the vascular membrane of the eye; it accounts for approximately 10–15 % of complete blindness cases and up to 20 % of officially confirmed blindness in the developed world [1, 2]. SpA comprises ankylosing arthritis (AS), psoriatic arthritis (PsA), arthritis of inflammatory bowel disease (AIBD), reactive arthritis (ReA), juvenile spondylitis (jSpA), and undifferentiated spondyloarthritis (uSpA). These conditions may exhibit a similar clinical pattern and common pathophysiological mechanisms [3]. Uveitis is considered to be one of the most common extra-articular manifestations of SpA and was reported in up to 30 % of AS cases [4].

Similar to other non-infectious uveitis, SpA-related uveitis generally has an acute onset that is typically marked with a red and painful eye and may be accompanied by photophobia, hyperlacrimation, and blurred vision. Uveitis is likely to complicate sight threatening situations such as glaucoma and cystoid macular edema [5, 6], thereby resulting in vision loss.

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Uveitis is strongly associated with HLA-B27. Up to 30 to 50 % of patients with positive HLA-B27 will suffer uveitis during the course of their diseases. HLA-B27 positivity was linked to worse prognosis and stronger tendency toward relapses. Conversely, uveitis with positive HLA-B27 is more likely to be associated with sacroiliitis and/or peripheral arthritis [6–10].

Corticosteroid and conventional immunosuppressive agents including methotrexate (MTX) were used for SpA-related uveitis for several decades [11]. Biological modifiers such as TNF-α inhibitors were shown to be effective [12–14]. Regarding SpAs, TNF-α inhibitors contribute to the substantial improvements of both articular manifestations and uveitis.

In this study, we summarized the clinical features of SpA related uveitis in a population from southern China and evaluated the efficacy and safety of TNF-α inhibitors plus MTX as well as the differences between the three most commonly used anti-TNF agents in the study group in an assessment of the therapeutic strategies.

Patients and methods

All patients were consecutively recruited from January 2012 to March 2014 at the First Affiliated Hospital of Sun Yat-set University and the retrospective chart review study was conducted.

The diagnosis of SpA was based on the Assessment of Spondyloarthritis International Society (ASAS) classification criteria [15–17]. The diagnosis of uveitis was principally based on clinical manifestations [18, 19].

The SpA-related uveitis cases recruited in this study were diagnosed on the first admission to our hospital before treatments of methotrexate, sulphasalazine, or anti-tumor necrosis factor alpha. And the diagnosis was made or confirmed by both rheumatologists and ophthalmologists. Patients with Beh et disease, Vogt–Koyanagi–Harada syndrome, or another type of uveitis were excluded; patients were excluded if they had virus hepatitis or tuberculosis before treatments of methotrexate and anti-tumor necrosis factor alpha at the first time they admitted to the clinic; patients with active inflammation, other rheumatologic diseases, or malignancy were also excluded.

Clinical parameters, laboratory results, and radiological findings were recorded.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), and Bath Ankylosing Spondylitis Functional Index (BASFI) were documented [20–23].

Etanercept was administered subcutaneously (s.c.) twice a week at a dosage of 25 mg. Adalimumab was administered subcutaneously at a dosage of 40 mg every other week. Infliximab was infused at weeks 0, 2, 6, and 14 and every other 8 weeks as directed. Methotrexate was administered subcutaneously once a week at a dosage of 10–15 mg.

Intraocular inflammation, visual acuity, and macular thickness were measured as the ocular variables. Inflammatory activity was graded from 0 to 4 according to the Standardization of Uveitis Nomenclature (SUN) criteria [24]. Improvement in inflammation was defined as a two-step decrease or to grade 0. Worsening of inflammation was defined as a two-step increase or an increase from grade 3 to 4.

The best-corrected visual acuity (BCVA) was evaluated according to the Age Related Eye Disease Study adapted ETDRS protocol [25]. Worsening or improvement of BCVA was defined as three lines (±0.3 logMAR; ±15 letters) of change. Macular thickness was measured by optical coherence tomography (OCT). Cystoid macular edema (CME) was evaluated in the mean 1 mm central foveal retina [26].

Statistical analysis

Categorical data are expressed as absolute number and percentages and continuous data as the mean±SD. Chi-squared test was used to compare categorical variables. The Mann–Whitney U test and t test were used to compare continuous variables.

Statistical analyses were performed using SPSS 16.0. Statistical significance was defined as $p<0.05$.

Results

A total of 1,036 Asian spondyloarthropathy (SpA) patients were reviewed in the study, including 788 (76.1 %) cases of ankylosing spondylitis, which was the most common subtype, 102 cases of reactive arthritis (9.8 %), 32 (3.1 %) cases of inflammatory bowel disease arthritis, 68 (6.6 %) cases of psoriatic arthritis, and 46 (4.4 %) cases of undifferentiated spondyloarthritis. SpA-related uveitis was diagnosed in 182 cases (17.6 %). The demographic and clinical characteristics of the SpA-related uveitis patients are listed in Tables 1 and 2.

All patients were followed for at least 6 months. The majority of patients were young and male. The mean age at uveitis onset was 21.3±8.7 years. The median time between the diagnosis of SpA and uveitis was 4 months, with a range from 0 to 107 months. HLA-B27 was positive in 167 cases (91.8 %).

Most patients presented with arthritis (153/182, 84.1 %). Unilateral uveitis was found in 51 cases (51/182, 28.0 %) and unilateral alternating uveitis was found in 75 cases (75/182, 41.2 %) on the first admission to our hospital before treatments of methotrexate, sulphasalazine, or anti-tumor necrosis factor alpha. Altogether, 238 eyes were involved (126 eyes of unilateral uveitis cases plus 112 eyes of 56 cases with bilateral

Table 1 Demographic and clinical characteristics at baseline

	SpA-related uveitis (n=182)	SpA non-uveitis (n=854)	p value
Male, n (%)	153 (84.1)	756 (88.5)	>0.05
Age at SpA onset, years, mean±SD	20.4±8.9	22.6±18.1	>0.05
Disease duration, years, mean±SD	5.1±3.8	5.7±4.2	>0.05
CRP(mg/L), mean±SD	38.4±17.9	40.34±19.3	>0.05
ESR(mm/h), mean±SD	78.6±24.5	92.3±33.1	>0.05
HLA positive, n (%)	167 (91.8)	803(94.0)	>0.05
BASDAI (0–10)	6.6±2.8	5.9±3.1	>0.05
BASFI (0–10)	5.7±2.6	6.5±3.7	>0.05
ASDAS-CRP	2.4±0.6	2.2±0.5	>0.05
ASDAS-ESR	2.5±0.7	2.8±0.9	>0.05
SASDAS (0–10)	22.3±8.4	25.6±9.2	>0.05
Peripheral arthritis	78 (42.9 %)	588 (68.9 %)	>0.05

Abbreviations: *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *SADSAS* Simplified Ankylosing Spondylitis Disease Activity Score

uveitis). Half of the cases were recurrent uveitis (95/182, 52.2 %) on presentation, and acute onset was commonly observed (139/182, 76.4 %). The most serious complication was vision loss (1/182, 0.5 %). Reactive arthritis was more commonly associated with uveitis than other subtypes of SpA (30.4 %), followed by ankylosing spondylitis (17.1 %). The spectrum of eye involvement ranged from eye redness and pain, blurred vision, and light sensitivity to cataract, glaucoma, cystoid macular edema, and blindness. Anterior uveitis was the most common entity and was diagnosed in 136 eyes (136/238 eyes, 57.1 %). Laboratory findings showed an increased ESR and CRP in most patients, although no significant difference in disease activity was observed between the SpA patients with or without uveitis.

Table 2 Description of SpA-related uveitis

Characteristics	
uSpA, n (%)	5/46 (10.9)
Ankylosing spondylitis, n (%)	135/788 (17.1)
Reactive arthritis, n (%)	31/102 (30.4)
Psoriatic arthritis, n (%)	8/68 (11.8)
Inflammatory bowel disease arthritis, n (%)	3/32 (9.3)
Age at uveitis onset, years, mean±SD	21.2±10.3
Unilateral uveitis, n (%)	126 (69.2)
Bilateral uveitis, n (%)	56 (30.8)
Recurrent uveitis, n (%)	95 (52.2)
Eye redness and pain, n (%)	137/238 (57.6)
Light sensitivity, n (%)	45/238 (18.9)
Seclusion and pupillary occlusion	27/238 (11.3)
Low visual acuity, n of eyes (%)	49/238 (20.1)
Cataract, n of eyes (%)	53/238 (22.3)
Secondary glaucoma, n of eyes (%)	15/238 (6.3)
Cystoid macular edema, n of eyes (%)	5/238 (2.1)
Loss of vision, n (%)	1/238 (0.4)

The documented treatments included non-steroid anti-inflammatory drugs (for joint pain), topical corticosteroids, methotrexate, sulphasalazine, and anti-tumor necrosis factor alpha. Methotrexate and anti-TNF combination therapy was administered in 99 cases, including 55 cases of MTX plus etanercept (ETN), 32 cases of MTX plus adalimumab (ADA), and 12 cases of MTX plus infliximab (IFX).

The outcome measurements of different therapeutic strategies are compared and summarized in Table 3. Predominant improvements were found in cases treated with all three anti-TNFs and anti-TNFs plus MTX. A remarkable decrease in inflammation and macular thickness was observed, and visual acuity was significantly improved at the end of follow up. Treatment with methotrexate alone without TNF blockers was not adequate to induce remission.

With the comparison of different TNF blockers, we discovered that monotherapy with etanercept was not as effective as with adalimumab and infliximab, mainly in the prevention of recurrence (p<0.05, ETN versus ADA; p>0.05 ETN versus IFX). Although the difference between ETN and IFX did not reach statistical significance, the recurrence rate of ETN was much higher than that of IFX. However, combination therapy with etanercept and MTX largely improved therapeutic efficacy. ETN plus MTX achieved similar outcomes as the anti-TNF monoclonal antibodies. No significant difference in effectiveness was found among the three anti-TNFs if MTX was added.

Table 3 Treatment efficacy of anti-TNFs, MTX, and the combination therapy

	Week 0	Week 24	*p* value
MTX (37 cases)			
Anterior chamber inflammation	2.33±1.23	1.78±0.96	>0.05
Posterior chamber inflammation	2.89±1.71	2.03±1.81	>0.05
Macular thickness, μ	299.2±171.3	242.3±156.4	>0.05
Visual acuity improved, *n* (%)		1/5 (20.0)	
Relapse, *n* (%)		34/39 (87.2)	
MTX+ *ETN* (55 cases)			
Anterior chamber inflammation	2.46±1.13	0.53±0.57	<0.05
Posterior chamber inflammation	2.77±1.62	0.49±0.62	<0.05
Macular thickness, μ	332.2±189.7	212.6±134.5	<0.05
Visual acuity improved, *n* (%)		12/14 (85.7)	
Relapse, *n* (%)		6/53 (11.3)	
MTX+ *ADA* (32 cases)			
Anterior chamber inflammation	2.78±1.85	0.63±0.82	<0.05
Posterior chamber inflammation	2.89±1.93	0.58±0.67	<0.05
Macular thickness, μ	317.8±169.5	203.9±125.8	<0.05
Visual acuity improved, *n* (%)		7/9 (77.8)	
Relapse		3/32 (9.3)	
MTX+ *IFX* (12 cases)			
Anterior chamber inflammation	2.34±1.27	0.55±0.63	<0.05
Posterior chamber inflammation	2.66±1.58	0.41±0.59	<0.05
Macular thickness, μ	357±188.5	237±145.6	<0.05
Visual acuity improved, *n* (%)		4/5 (80.0)	
Relapse		2/12 (16.7)	
ETN (21 cases)			
Anterior chamber inflammation	2.25±1.16	0.73±0.95	<0.05
Posterior chamber inflammation	2.66±1.39	0.87±0.85	<0.05
Macular thickness, μ	323.6±166.4	249.8±129.6	<0.05
Visual acuity improved, *n* (%)		5/8 (62.5)	
Relapse		8/21 (38.1)	
ADA (16 cases)			
Anterior chamber inflammation	2.71±1.78	0.65±0.71	<0.05
Posterior chamber inflammation	2.33±1.59	0.49±0.59	<0.05
Macular thickness, μ	335.2±167.2	244.5±133.9	<0.05
Visual acuity improved, *n* (%)		3/5 (60.0)	
Relapse		1/16 (6.3)	
IFX (9 cases)			
Anterior chamber inflammation	2.53±1.66	0.38±0.54	<0.05
Posterior chamber inflammation	2.89±1.39	0.47±0.61	<0.05
Macular thickness, μ	355.1±173.2	210.9±111.4	<0.05
Visual acuity improved, *n* (%)		2/3 (66.7)	
Relapse		1/9 (11.1)	

Side effects

Methotrexate and etanercept were well tolerated in all patients during the follow up. One case of tuberculosis and one case of virus hepatitis flare were found in patients treated with adalimumab. Two cases of tuberculosis and one case of allergic shock were observed in the infliximab-treated patients. Severe infection was the major cause of therapy discontinuation. Minor side effects included localized rash at the site of rejection, a twofold increase in aminotransferase and slight dizziness.

Discussion

Uveitis is strongly associated with spondyloarthritis. As one of the most common extra-articular manifestations, it is highly responsible for reduced quality of life. In this paper, we summarized the main clinical and demographic characteristics of SpA-related uveitis in a southern Chinese population and assessed the therapeutic decisions and side effects accordingly to provide a better understanding of optimal treatment in future clinical practice.

A total of 1,036 Asian spondyloarthropathy (SpA) patients were reviewed in the study, among whom ankylosing spondylitis was the most common subtype, accounting for 76.1 % of the cases. Uveitis occurred in 17.6 % of all SpA patients. Reactive arthritis was highly prone to be complicated with uveitis (30.4 %), and inflammatory bowel disease arthritis represented the least possible subtype for the development of uveitis (9.3 %), which is mostly consistent with previous reports [27].

The symptoms of SpA-related uveitis were non-specific. It may precede or follow the onset of SpA, usually unilateral, which can alternate [28]. Uveitis may sometimes reveal a situation of formerly undiagnosed spondyloarthritis. It is necessary to search for evidence of associated HLA-B27 histocompatibility alleles or joint involvement in such patients if there are no arthritis complaints. In our study, we found a high frequency of HLA-B27 positive rate (91.8 %), which was in accordance with the previous study suggesting that uveitis is strongly associated with HLA-B27. HLA-B27 positivity was linked to worse prognosis and stronger tendency toward relapses. [6–10].

Research on correlation between HLA-B27 subtypes and AS showed that HLA-B*27:04, B*27:05, and B*27:02 were highly detected in Beijing Han population [29], and Qi J et al. discovered that AS patients with HLA-B*2705 demonstrated an older age of onset and had a higher risk of uveitis and dactylitis than did AS patients with HLA-B*2704 [30]. Further researches were required to explore the association between SpA-related uveitis and HLA-B27 subtypes.

Similar to previous research, acute anterior uveitis (AAU) was the most frequently observed. Better prognosis was observed in AAU of one episode without recurrence. Posterior uveitis and complications such as seclusion and pupillary occlusion, cataract, secondary glaucoma, and cystoid macular edema (CME) were much more common in prolonged and intractable cases [9]. Therefore, prompt and adequate treatment should be implemented for patients who do not respond well to topical corticosteroids or traditional slow-acting drugs to prevent the progression to a chronic course and severe complications.

The treatment strategy of SpA-related uveitis depends on the inflammation severity, uveitis recurrence, and medication response. Refractory uveitis was a driving force for intensive therapy. Anti-TNF-α drugs are recommended in cases of refractory uveitis and involvement of the posterior eye structures [31]. It is believed that TNF blockers have quick and sustained efficacy in treating SpA-related uveitis [32, 33].

The use of anti-TNF drugs in China has been increasing recently. The three available TNF blockers to date include infliximab, etanercept, and adalimumab. Etanercept and adalimumab have only been used for approximately 3 years in China. Nevertheless, very few papers have addressed anti-TNFs in the treatment of SpA-related uveitis in Chinese populations.

In our study, monotherapy with one of three TNF-α antagonists appears to have favorable efficacy, resulting in relief of ocular inflammation, decrease in macular thickness, and improvement of visual acuity. Similar effects were found for infliximab and adalimumab, although monotherapy with etanercept was not as effective as monotherapy with the other two agents, mainly in the prevention of recurrence. Our data were consistent with previous reports to some extent [34, 35], showing that etanercept was not as effective as infliximab and adalimumab.

However, we found that the combination therapy with etanercept and MTX substantially improved therapeutic efficacy. No significant difference in effectiveness was found among the three anti-TNFs if MTX was added. Methotrexate was the most commonly used traditional agent in uveitis, and it is considered to be relatively effective and with acceptable side effects [36]. However, the use of methotrexate in cases of AAU and SpA is controversial and not comprehensively studied [37]. Our data suggested that monotherapy with MTX has been discouraging. MTX did not induced remission or prevent recurrence in most cases. However, a strategy based on anti-TNFs in combination with MTX is a promising method of enhancing the therapeutic effects and sustaining improvement.

Given the cost of TNF blockers, they may be considered unaffordable by some patients or would sometimes only be selected when refractory uveitis persists for at least 3 months. MTX is also an option for maintenance therapy for preventing uveitis relapses in previously controlled patients in whom tapering of TNF blockers is being attempted.

Topical steroids were effective in some cases and would not be excluded if uveitis continued in the course of during anti-TNFα agents and/or MTX treatment.

From the retrospective review of the records, steroids reduction in patients with great improvements on anti-TNFα agents plus MTX treatment would not negatively influence the outcome. Indeed, most patients received anti-TNFα agents plus MTX experienced a quick improvement and topical steroids could be reduced or stopped.

A large proportion of the SpA patients included in this study as we observed, uveitis was not the only symptom they complained. Spondylarthritis and joint pain may also be the

main reasons to come to clinic and some of the patients had inflammatory bowel disease or psoriasis. Biologics or adding MTX may be started as first line treatment targeting other lesions (not only for uveitis) of SpA and they were useful for uveitis as well, and the regimen sometimes was so effective that the topical steroids could be largely reduced very soon or declined by the patients.

TNF blockers were well tolerated in general. In our cases, etanercept did not trigger severe infection or liver dysfunction, and the combinations with MTX did not increase such side effects. Both infliximab and adalimumab were associated with tuberculosis and/or hepatitis flares, although these side effects occurred sporadically. Infliximab caused one serious allergic shock case.

Anti-TNF-α therapy may expose patients to an increased risk of developing infection, especially tuberculosis. From the previous study, Atteno M et al. showed that different anti-TNF-α agents (ETN vs. ADA) were both effective and safe in PsA patients with concomitant LTB in Naples [38]. However, China is a country with high incidence of tuberculosis. The use of anti-TNF-α agents increases the incidence/risk of TB. Published data suggested that the risk of TB may be less with etanercept than with the monoclonal antibodies infliximab and adalimumab [39, 40]. Our study observed one case of tuberculosis and one case of virus hepatitis flare in patients treated with adalimumab while methotrexate and etanercept were well tolerated. On the other hand, etanercept adding methotrexate was as effective as treatments containing adalimumab in the present research. We have to consider the rate of risked return given the higher risk of TB which is endemic in China. This difference between etanercept and the monoclonal antibodies may be more substantial and clinically meaningful.

The use of TNFα inhibitors also raised concerns of other infections. Regarding to HBV infection, there were different opinions. Biondo MI et al. confirms the substantial safety of anti-TNFα therapy in potential occult HBV carriers RA and SpA patients [41]. Carroll et al. concluded that etanercept is relatively safer than monoclonal antibodies because of its unique chemical structure and mechanism of action [42]. Although there is no consensus about the use of TNFα inhibitors in patients with chronic HBV infection, HBV screening and HBV status monitoring status are necessary weighing the potential risks [43, 44].

Regarding to HCV infection, national surveys in 1992 and 2006 showed a decline of HCV infection from 3.2 to 0.43 % in the general population in China[45, 46], and no HCV-infected patient was found in our study. Costa L et al. and Caso F et al. suggested anti-TNF-α agents are effective and safe in PsA patients with concomitant HCV [47, 48]. From the present study, we did not have much knowledge of concomitant HCV patients treated with TNF-α inhibitors. However, considering the low prevalence of HCV infection in China, as well as the data of previous studies, HCV infection may not be a tremendous hinder of anti- TNF-α treatment.

China is a country with a high burden of tuberculosis and type B hepatitis. Etanercept and MTX combination therapy would appear to be preferred above the other two TNF blockers due to concerns regarding their safety profiles. Monoclonal antibodies should be used with caution in high-risk patients. Furthermore, etanercept plus MTX may be an ideal alternative for patients who are well controlled with infliximab and for whom a switch from intravenous infusions to subcutaneous injections is planned.

In conclusion, uveitis is common in SpA patients. Severe complications may develop in prolonged and intractable cases. Early diagnosis and effective treatment result in better prognosis. We evaluated the three available TNF blockers. Good clinical response and better safety profile were observed with etanercept combination therapy with MTX compared to the other two anti-TNF monoclonal antibodies. Our study was retrospective and too small to draw definitive conclusions. More detailed and comprehensive studies are required.

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Disclosures None.

Reference

1. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P et al (2004) Degree, duration, and causes of visual loss in uveitis. Br J Ophthalmol 88:1159–1162
2. Gritz DC, Wong IG (2004) Incidence and prevalence of uveitis in Northern California; the Northern California Epidemiology of Uveitis Study. Ophthalmology 111:491–500
3. Liao S, Pan YF, Huang JL et al (2009) An epidemiological survey of low back pain and axial spondyloarthritis in a Chinese Han population. Scand J Rheumatol 38(6):455–459
4. Brophy S, Calin A (2001) Ankylosing spondylitis: interaction between genes, joints, age at onset, and disease expression. J Rheumatol 28:2283–2288
5. Hajj-Ali RA, Lowder C, Mandell BF (2005) Uveitis in the internist's office: are a patient's eye symptoms serious? Cleve Clin J Med 72:329–339
6. Rosenbaum JT (1992) Acute anterior uveitis, and spondyloarthropathies. Rheum Dis Clin North Am 18:143–151
7. Laval SH, Timms A, Edwards S, et al. (2001) Whole-genome screening in ankylosing spondylitis: evidence of non-MHC genetic-susceptibility loci. Am J Hum Genet 68(4):918–926
8. Gran J, Skomsvoll J (1997) The outcome of ankylosing spondylitis: a study of 100 patients. Rheumatology 15:766–771
9. Chang JH, McCluskey PJ, Wakefield D (2005) Acute anterior uveitis and HLA-B27. Surv Ophthalmol 15:364–388
10. Braun J, Baraliakos X, Listing J, Sieper J (2005) Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. Arthritis Rheum 15:2447–2451

11. Pasadhika S, Rosenbaum JT (2014) Update on the use of systemic biologic agents in the treatment of noninfectious uveitis. Biologics 8:67–81
12. Santos Lacomba M, Marcos Martı´n C, Gallardo Galera JM et al (2001) Aqueous humor and serum tumor necrosis factor-alpha in clinical uveitis. Ophthalmic Res 33:251–255
13. De Smet MD (2006) RESCU participants. Infliximab for uveitis: forty six week efficacy and safety results from the Remicade European Study for Chronic Uveitis (RESCU). Inv Ophthalmol Vis 47: E-Abstract, 1525.
14. Guignard S, Gossec L, Salliot C et al (2006) Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondyloarthropathy: a retrospective study. Ann Rheum Dis 65: 1631–1634
15. Sieper J, Rudwaleit M, Khan MA, Braun J (2006) Concepts and epidemiology of spondyloarthritis. Best Pract Res Clin Rheumatol 20:401–417
16. Rudwaleit M, van der Heijde D, Landewe R et al (2011) The Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarrhtiritis in general. Ann Rheum Dis 70:25–31
17. Sieper J, Rudwaleit M, Baraliakos X, et al. (2009) The Assessment of Spondyloarthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 68 Suppl 2
18. Rothova A, van Veenedaal WG, Linssen A, Glasius E, Kijlstra A, de Jong PT (1987) Clinical features of acute anterior uveitis. Am J Ophthalmol 15:137–145
19. Miettinen R, Saari M (1977) Clinical characteristics of familial acute anterior uveitis. Can J Ophthalmol 15:1–3
20. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A (1994) A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondilytis Disease Activity Index. J Rheumatol 21:2286–2291
21. Calin A, Garrett S, Whitelock H et al (1994) A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 21:2281–2285
22. Jenkinson TR, Mallorie PA, Whitelock H, Kennedy LG, Garrett S, Calin A (1994) Defining spinal mobility in ankylosing spondylitis (AS): the Bath AS Metrology Index. J Rheumatol 21:1694–1698
23. van der Heijde D, Lie E, Kvien TK et al (2009) ASDAS, a highly discriminatory ASAS endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 68:1811–1818
24. Jabs DA (2005) Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol 140(3):509–516
25. Age-Related Eye Disease Study Research Group (1999) The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no.1 Control. Control Clin Trials 20(6):573–600
26. Nussenblatt RB, Peterson JS, Foster CS et al (2005) Initial evaluation of subcutaneous daclizumab treatments for noninfectious uveitis: a multicenter noncomparative interventional case series. Ophthalmology 112(5):764–770
27. Sampaio-Barros PD, Pereira IA, Hernandez-Cuevas C et al (2013) An analysis of 372 patients with anterior uveitis in a large Ibero-American cohort of spondyloarthritis: the RESPONDIA Group. Clin Exp Rheumatol 31(4):484–489
28. McCannel CA, Holland GN, Helm CJ, Cornell PJ, Winston JV, Rimmer TG (1996) Causes of uveitis in the general practice of ophthalmology. Am J Ophthalmol 121(1):35–46
29. Zhang Z, Dai D, Yu K, Yuan F, Jin J, Ding L, Hao Y, Liang F, Liu N, Zhao X, Long J, Xi Y, Sun YY (2014) Association of HLA-B27 and ERAP1 with ankylosing spondylitis susceptibility in Beijing Han Chinese. Tissue Antigens 83(5):324–329
30. Qi J, Li Q, Lin Z, Liao Z, Wei Q, Cao S, Rong J, Hu Z, Yang M, Zhang Y, Lv Q, Huang J, Pan Y, Wu Y, Jin O, Li T, Gu J (2013) Higher risk of uveitis and dactylitis and older age of onset among ankylosing spondylitis patients with HLA-B*2705 than patients with HLA-B*2704 in the Chinese population. Tissue Antigens 82(6):380–386
31. Levy-Clarke G, Nussenblatt R (2006) Does anti-TNF therapy decrease the incidence of anterior uveitis in patients with ankylosing spondylitis? Nat Clin Pract Rheumatol 2(2):72–73
32. Greiner K, Murphy CC, Willermain F, Duncan L, Plskova J, Hale G et al (2004) Anti-TNF-alpha therapy modulates the phenotype of peripheral blood CD4+ T cells in patients with posterior segment intraocular inflammation. Invest Ophthalmol Vis Sci 45(1):170–176
33. Neri P, Zucchi M, Allegri P, Lettieri M, Mariotti C, Giovannini A (2011) Adalimumab (HumiraTM): a promising monoclonal anti-tumor necrosis factor alpha in ophthalmology. Int Ophthalmol 31(2):165–173
34. Galor A, Perez VL, Hammel JP, Lowder CY (2006) Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. Ophthalmology 113(12):2317–2323
35. Foster CS, Tufail F, Waheed NK et al (2003) Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. Arch Ophthalmol 121(4):437–440
36. Gangaputra S, Newcomb CW, Liesegang TL et al (2009) Methotrexate for ocular inflammatory diseases. Ophthalmology 116(11):2188–2198
37. Muñoz-Fernández S, García-Aparicio AM, Hidalgo MV et al (2009) Methotrexate: an option for preventing the recurrence of acute anterior uveitis. Eye (Lond) 23(5):1130–1133
38. Atteno M, Costa L, Matarese A, Caso F, Del Puente A, Cantarini L, Bocchino ML, Sanduzzi A, Scarpa R (2014) The use of TNF-α blockers in psoriatic arthritis patients with latent tuberculosis infection. Clin Rheumatol 33(4):543–547
39. Tubach F, Salmon D, Ravaud P et al (2009) Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum 60:1884–1894
40. Dixon WG, Hyrich KL, Watson KD et al (2010) Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 69: 522–528
41. Biondo MI, Germano V, Pietrosanti M, Canzoni M, Marignani M, Stroffolini T, Salemi S, D'Amelio R (2014) Lack of hepatitis B virus reactivation after anti-tumour necrosis factor treatment in potential occult carriers with chronic inflammatory arthropathies. Eur J Intern Med 25(5):482–484
42. Carroll MB, Bond MI (2008) Use of tumor necrosis factor-α inhibitors in patients with chronic hepatitis B infection. Semin Arthritis Rheum 38:208–217
43. Calabrese LH, Zein NN, Vassilopoulos D (2006) Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. Ann Rheum Dis 65: 983–989
44. Nathan DM, Angus PW, Gibson PR (2006) Hepatitis B and C virus infections and anti-tumor necrosis factor-α therapy: guidelines for clinical approach. J Gastroenterol Hepatol 21:1366–1371
45. Xia GL, Liu CB, Cao HL, Bi SL, Zhan MY, Su CA et al (1996) Prevalence of hepatitis B and C virus infections in the general Chinese population: results from a nationwide cross-sectional seroepidemiologic study of hepatitis A, B, C, D, and E virus infections in China, 1992. Int Hepatol Commun 5(1):62–73
46. Chen YS, Li L, Cui FQ, Xing WG, Wang L, Jia ZY et al (2011) A sero-epidemiological study on hepatitis C in China. Chin J Epidemiol 32(9):888–891

47. Costa L, Caso F, Atteno M, Giannitti C, Spadaro A, Ramonda R, Vezzù M, Del Puente A, Morisco F, Fiocco U, Galeazzi M, Punzi L, Scarpa R (2014) Long-term safety of anti-TNF-α in PsA patients with concomitant HCV infection: a retrospective observational multicenter study on 15 patients. Clin Rheumatol 33(2):273–276

48. Caso F, Cantarini L, Morisco F, Del Puente A, Ramonda R, Fiocco U, Lubrano E, Peluso R, Caso P, Galeazzi M, Punzi L, Scarpa R, Costa L (2015) Current evidence in the field of the management with TNF-α inhibitors in psoriatic arthritis and concomitant hepatitis C virus infection. Expert Opin Biol Ther 15(5):641–650