



# Optical coherence tomography changes in ankylosing spondylitis patients on long-term adalimumab treatment

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## SUMMARY

**OBJECTIVE:** Long-term ocular effects of tumor necrosis factor-alpha inhibitors remain to be elucidated. This study aimed to examine the long-term effects of adalimumab use on neural tissue of the anterior visual pathways using optical coherence tomography in patients with ankylosing spondylitis.

**METHODS:** This was a single-center, open-label, cross-sectional study conducted at the Giresun University Faculty of Medicine, Physical Medicine and Rehabilitation Department, between November 2019 and August 2020. This study included 26 ankylosing spondylitis patients receiving adalimumab for at least 1 year and 21 healthy controls. All subjects underwent a full ophthalmological examination and optical coherence tomography examination with the following measurements: peripapillary retinal nerve fiber layer thickness, peripapillary retinal thickness, peripapillary choroidal thickness, ganglion cell complex thickness, and the optic head properties.

**RESULTS:** Peripapillary retinal nerve fiber layer thickness and retinal thickness measurements were lower in the adalimumab group. In addition, ganglion cell complex thickness was significantly lower and the cup-to-disc ratio was significantly higher in the adalimumab group ( $p < 0.05$ ). However, the two groups did not differ in terms of peripapillary choroidal thickness and disc area ( $p > 0.05$ ).

**CONCLUSION:** Although tumor necrosis factor-alpha inhibitors have some favorable effects on the ocular involvement of patients with ankylosing spondylitis, they may also have paradoxical detrimental effects as evidenced by structural changes observed by optical coherence tomography. Future studies with better design, probably including a large number of patients with a range of rheumatological diseases and tumor necrosis factor-alpha inhibitors, are warranted.

**KEYWORDS:** Tumor necrosis factor alpha. Adalimumab. Optical coherence tomography.

## INTRODUCTION

Ankylosing spondylitis, a form of axial spondyloarthritis (SpA), is a chronic inflammatory rheumatic disease and manifests itself by inflammatory back pain, radiographic sacroiliitis, and excess spinal bone formation, as well as non-skeletal manifestations such as uveitis, inflammatory bowel disease (IBD), or psoriasis<sup>1</sup>. Reported prevalence rates range between 0.1 and 0.5%<sup>1,2</sup>.

Tumor necrosis factor-alpha (TNF-alpha) is a cytokine with a key regulatory role in the inflammatory response, and impaired regulation of TNF-alpha has been suggested to have a role in the pathogenesis of inflammatory conditions. Blocking the action of TNF-alpha has been used in the treatment of chronic inflammatory conditions, including ankylosing spondylitis. Adalimumab is a recombinant human IgG1 monoclonal antibody, specific for human TNF-alpha.

Despite its revolutionary benefits in rheumatologic disease, adverse effects such as ocular complications, severe infection,

demyelinating conditions, malignancies, a lupus-like syndrome, induction of autoantibodies, injection site reactions, and heart failure have been reported with the use of TNF-alpha inhibitors<sup>3</sup>. Reported ocular side effects include periorbital infection, oculomotor nerve palsy, optic neuritis, central vein occlusion, as well as a paradoxical adverse event uveitis<sup>4-8</sup>. Most data on ocular side effects come from anecdotal reports, and pathophysiological processes are mostly unknown<sup>3</sup>; thus, ocular structural changes during long-term TNF-alpha inhibitor use may shed light on the pathogenesis of these conditions.

Optical coherence tomography (OCT) is a practical technique widely used in clinical practice, which enables detailed examination of the eye and allows the thicknesses of the choroid, retina, and peripapillary retinal nerve fiber layer (RNFL) to be measured.

This study aimed to examine the potential long-term adverse effects of adalimumab use on neural tissue of the anterior visual

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pathways through the measurements of peripapillary RNFL thickness, peripapillary retinal and choroidal thicknesses, optic nerve parameters, and ganglion cell complex (GCC), using OCT.

## METHODS

The study protocol was approved by the Institutional Review Board of Hatay Mustafa Kemal University Medical Faculty (date June 3, 2021, number 07), and the study followed the tenets of the Declaration of Helsinki.

A total of 26 eyes of 26 ankylosing spondylitis patients on adalimumab attending the outpatient clinics of the Physical Therapy and Rehabilitation department (adalimumab group) and 21 eyes of 21 healthy controls were included in this single-center, open-label, cross-sectional study. All eyes underwent a full ophthalmological examination including refractive measurements with an autorefractor (Topcon Auto Ref-Keratometer, Tokyo, Japan), best corrected visual acuity (BCVA) evaluation, intraocular pressure measurements, biomicroscopic evaluation with slit-lamp examination, and OCT examination. Considering that outcome measurements from both eyes of the same subject tend to be positively correlated<sup>9</sup>, the right eye was selected for study measurements if both eyes were suitable for inclusion.

According to inclusion criteria, patients had to fulfill modified New York diagnostic criteria for ankylosing spondylitis, had to be >18 years of age, and should be receiving adalimumab for at least 1 year and provide informed consent. The patients attending the outpatient clinics of Giresun University Faculty of Medicine, Physical Medicine and Rehabilitation Department between November 2019 and August 2020 were included. Exclusion criteria were as follows: additional systemic disease, previous intraocular surgery or intracranial surgery, previous history of optic disc edema, and the presence of glaucoma and/or ocular hypertension, papillitis, or any other retinal disease.

In all, 21 patients without any systemic disease or ocular pathology who applied to the Physical Therapy and Rehabilitation outpatient department for other reasons were served as controls. Written informed consent was obtained from all subjects prior to the study.

Patients were receiving 40 mg of subcutaneous adalimumab every other week for at least 1 year and all were under remission (BASDAI<4) for at least 6 months. None of them were receiving concomitant glucocorticoids.

All eyes were examined by a spectral domain OCT device (Retinascan Advanced RS-3000; NIDEK, Gamagori, Japan). All OCT examinations were done by an investigator blinded to the patient groups, analyzed, and interpreted by using a software (NAVIS-EX, NIDEK, Tokyo, Japan). The following measurements were taken:

- **Peripapillary RNFL thickness** In the peripapillary region, a circular 3.45-mm diameter scan centered over the optic disc was used to measure RNFL thickness (using “disc circle” option). Average peripapillary RNFL thickness (360°) as well as peripapillary RNFL thicknesses at superior (46°–135°), inferior (226°–315°), nasal (136°–225°), and temporal (316°–45°) quadrants were measured.
- **Peripapillary retinal thickness** Using the same image and manually changing the lower border as the retina pigment epithelium, the average peripapillary retinal thickness (RT) and RTs at the superior, nasal, inferior, and temporal quadrants were measured. The temporal-superior-nasal-inferior thickness (TSNIT) graph (ILM-RPE/BM) was automatically displayed after this manual marking.
- **Peripapillary choroidal thickness** The average peripapillary choroidal thickness and peripapillary choroidal thicknesses of the four quadrants were estimated using the image obtained by the inversion of the peripapillary region image. Again, a circular 3.45-mm diameter scan centered over the optic disc was used with the “disc circle” option. The scans consisted of 1,024 “A scans” of high-definition (50 HD) frame enhancement software. To improve the choroidal image, the OCT device located the inversed image in closer proximity to the zero-delay line and displayed it on the upper part of the monitor. The outer border of the hyper-reflective retinal pigment epithelium (RPE/BM) was displayed automatically, and the sclera-choroidal vertical distance was manually drawn. The TSNIT graph (RPE/BM-manual [choroid]) was created automatically using the software.
- **GCC thickness and the optic head** Macula map X-Y (6.0–6.0 mm [256–256]) of the OCT device was used for GCC thickness map (ILMIPL/INL), and disc map X-Y (6.0–6.0 mm [256–256]) setting was used for optic nerve head properties.
- **Statistical analysis** The SPSS (Statistical Package for Social Sciences) software version 27.0 was used for statistical analyses. Descriptive data were presented as mean±standard deviation, median (range), and frequency (percentage), where appropriate. The normality of the data was tested using the Kolmogorov-Smirnov test. Independent samples t-test and Mann-Whitney U test were used for the comparison of quantitative data, depending on the distribution. A chi-square test was used for the comparison of qualitative data.

## RESULTS

### Patient characteristics

Table 1 shows the comparisons of the demographic and clinical characteristics. The groups did not differ in terms of age, gender distribution, distribution of the included eye (right or left), visual acuity, intraocular pressure, or spherical equivalent ( $p > 0.05$  for all comparisons).

### OCT findings

Table 2 summarizes the OCT findings of the two groups. The average peripapillary RNFL thickness was significantly lower in the adalimumab group compared to that of the controls ( $p < 0.001$ ). In addition, the former group had lower RNFL measurements in all four quadrants ( $p < 0.05$  for all). However, the two groups did not differ in terms of peripapillary choroidal thickness ( $p > 0.05$  for all). The adalimumab group had significantly lower average peripapillary RT measurements ( $p < 0.05$ ) than controls, and this relationship was true for all ( $p < 0.05$ ) but the nasal quadrant ( $p = 0.115$ ).

The GCC thickness was significantly lower (in both superior and inferior) and the cup-to-disc ratio (both horizontal and vertical) was significantly higher in the adalimumab group ( $p < 0.05$  for all). Although the average cup area was higher in the adalimumab group ( $p < 0.05$ ), the two groups did not differ in terms of disc area ( $p = 0.358$ ).

## DISCUSSION

In our study examining the potential effects of adalimumab use for a relatively long duration, we identified negative effects on several OCT parameters; however, such an effect does not seem to translate into significant ophthalmological problems, at least within 1 year, as evidenced by no change in visual acuity, spherical equivalents, or intraocular pressure. To the best of our knowledge, this is the first study to examine the effects

of longer adalimumab use on OCT parameters in comparison to healthy controls.

There is only one study in the literature examining the effect of TNF-alpha inhibitors on OCT findings in patients with ankylosing spondylitis<sup>10</sup>. In that 2015 study, 21 nonresponsive patients to non-steroidal anti-inflammatory drugs (NSAIDs) and sulfasalazine received one of the three TNF-alpha inhibitors (etanercept, adalimumab, or infliximab) and were followed with OCT measurements for peripapillary RNFL, GCIPL, and macular thickness. During the 6-month follow-up, no significant difference was detected in OCT parameters or intraocular pressure, although the treatment was effective in disease control. The authors concluded that TNF-alpha blockage does not influence the measured OCT parameters in patients with ankylosing spondylitis, at least in the short term. Those findings are in contrast with the findings of the present study, which found significant changes in OCT findings of ankylosing spondylitis patients receiving adalimumab for at least 1 year. There may be several explanations for such a difference. First, in that study, 21 patients received three different TNF-alpha inhibitors and only 7 patients received adalimumab. Less number of patients in the whole study group might have prevented to reach adequate statistical power. In addition, such a design with less number of patients receiving adalimumab may not be adequate for the determination of drug-specific effects on OCT findings. Second, 6-month follow-up may not be sufficient to detect any effect. On the contrary, our design may not be able to differentiate between disease- and drug-specific effects, since it did not include ankylosing spondylitis patients not receiving adalimumab or a TNF-alpha inhibitor; rather, our controls were healthy individuals. Thus, studies with a more detailed design and longer follow-up are required to examine any potential effects of TNF-alpha inhibitors in general, particularly adalimumab.

TNF-alpha is a cytokine with roles in the inflammatory processes. Understanding its key role in the pathogenesis of autoinflammatory diseases paved the way to the development

**Table 1.** Demographic and clinical features of the groups.

	Adalimumab group (n=26)	Control group (n=21)	p-value
Age, years	45.3 (9.6)	40.5 (12.1)	0.141 <sup>t</sup>
Male gender, n (%)	17 (65.4)	13 (61.9)	0.805 <sup>x</sup>
Right eye, n (%)	20 (76.9)	16 (76.2)	0.953 <sup>x</sup>
BCVA	1.00 (0.10)	1.00 (0.00)	0.122 <sup>m</sup>
SE, diopter	0.00 (1.00)	0.00 (1.13)	0.786 <sup>m</sup>
IOP, mmHg	13.50 (5.25)	13.00 (5.00)	0.620 <sup>m</sup>

BCVA: best corrected visual acuity; SE: spherical equivalent; IOP: intraocular pressure; M/F: male/female; R/L: right/left. Unless otherwise stated, data presented as mean (standard deviation) for parametric test and median (interquartile range) for nonparametric test. <sup>t</sup>t-test; <sup>m</sup>Mann-Whitney U test; <sup>x</sup> $\chi^2$  test.

**Table 2.** Comparison of the groups for optical coherence tomography parameters.

	Adalimumab group (n=26)	Control group (n=21)	p-value
RNFL thickness (µm)			
Average	89.9 (10.1)	107.2 (7.8)	<b>&lt;0.001<sup>t</sup></b>
Superior	121.1 (17.9)	136.4 (13.0)	<b>&lt;0.05<sup>t</sup></b>
Nasal	61.7 (9.8)	77.5 (8.2)	<b>&lt;0.001<sup>t</sup></b>
Inferior	119.5 (13.2)	139.3 (11.8)	<b>&lt;0.001<sup>t</sup></b>
Temporal	66.0 (10.8)	75.1 (7.6)	<b>&lt;0.05<sup>t</sup></b>
Choroidal thickness (µm)			
Average	191.2 (9.2)	193.6 (12.4)	0.437 <sup>t</sup>
Superior	189.0 (7.8)	190.5 (10.7)	0.341 <sup>t</sup>
Nasal	186.8 (8.5)	188.4 (13.1)	0.655 <sup>t</sup>
Inferior	187.2 (8.7)	188.8 (9.0)	0.251 <sup>t</sup>
Temporal	193.9 (11.2)	191.3 (10.1)	0.399 <sup>t</sup>
Retinal thickness (µm)			
Average	310.7 (14.8)	336.3 (11.7)	<b>&lt;0.05<sup>t</sup></b>
Superior	324.1 (10.8)	330.3 (10.1)	<b>&lt;0.05<sup>t</sup></b>
Nasal	315.5 (11.5)	321.3 (11.7)	0.115 <sup>t</sup>
Inferior	314.1 (14.8)	344.7 (13.1)	<b>&lt;0.05<sup>t</sup></b>
Temporal	305.0 (16.1)	335.7 (10.8)	<b>&lt;0.05<sup>t</sup></b>
GCC thickness (µm)			
Superior	85.9 (14.3)	104.7 (7.9)	<b>&lt;0.001<sup>t</sup></b>
Inferior	87.5 (13.9)	107.7 (8.8)	<b>&lt;0.001<sup>t</sup></b>
Cup-to-disc ratio			
Horizontal	0.491 (0.182)	0.385 (0.116)	<b>&lt;0.05<sup>t</sup></b>
Vertical	0.513 (0.221)	0.397 (0.137)	<b>&lt;0.05<sup>t</sup></b>
Average cup area (mm <sup>2</sup> )	0.837 (0.49)	0.638 (0.291)	<b>&lt;0.05<sup>t</sup></b>
Disc area (mm <sup>2</sup> )	2.396 (0.604)	2.481 (0.454)	0.358 <sup>t</sup>

OCT: optical coherence tomography; RNFL: retinal nerve fiber layer; GCC: ganglion cell complex. Data presented as mean (standard deviation) for parametric test and median (interquartile range) for nonparametric test. <sup>t</sup>t-test. Bold values indicate statistical significance.

of biological treatments for the blockade of TNF-alpha with good treatment responses. They have been found effective for the extra-articular involvement of rheumatological disease including the eye as well as for musculoskeletal manifestation<sup>1,11,12</sup>. For example, noninfectious uveitis attacks can develop during autoinflammatory diseases such as ankylosing spondylitis or Behçet's disease, where disease activity seems to be correlated with TNF-alpha. Adalimumab, a recombinant human immunoglobulin G1 monoclonal antibody specifically binding TNF-alpha, has been shown to be effective in the treatment of intermediate, noninfectious posterior uveitis and panuveitis cases. In the VISUAL III study, intraocular inflammation was better controlled and systemic steroid use was reduced in patients with active and inactive noninfective uveitis who received adalimumab for more than 78 weeks<sup>12</sup>.

TNF-alpha antagonist may be associated with paradoxical adverse events, including uveitis<sup>8</sup>. However, in such cases, infectious conditions such as tuberculosis should be ruled out. Several other ocular conditions such as severe inflammation of the orbit have been reported in association with adalimumab<sup>4</sup>. Optical neuritis leading to irreversible vision loss may also develop in association with anti-TNF-alpha treatments. In a study with 68 multiple sclerosis patients receiving anti-TNF-alpha treatment, more recurrences were observed when compared to the controls<sup>13</sup>.

Changes in OCT findings in association with adalimumab use found in this study potentially suggest a neurotoxic side effect. Although rare, TNF-alpha inhibition-related neurotoxicities/neuropathies, such as multiple sclerosis, Guillain-Barre and Miller-Fischer syndrome, chronic inflammatory demyelinating

peripheral neuropathy, mononeuropathy simplex, mononeuropathy multiplex, and multifocal motor neuropathy, have been reported, mostly in case reports<sup>14</sup>. In a large safety analysis of adalimumab, it is estimated that the incidence of demyelinating disorders is less than 0.1 per 100 patient-years<sup>15</sup>. The fact that functional impairment in vision was not evaluated in this study highlights the need for a more detailed investigation of such a potential effect. The decrease in apoptosis of retinal ganglion cells with neutralizing antibodies against TNF- $\alpha$ <sup>16</sup> also weakens the claim that inhibition of TNF- $\alpha$  may have a direct detrimental effect on retinal nerves.

This study has several limitations. First, a control group consisting of ankylosing spondylitis patients who did not receive adalimumab would explain whether any change is associated with the disease itself. Second, a prospective design would elucidate the relation of any changes with time. Finally, a design with a larger number of participants would improve study power.

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## CONCLUSION

Although TNF- $\alpha$  inhibitors have some favorable effects on the ocular involvement of patients with ankylosing spondylitis, they may also have detrimental effects, some of which may be paradoxical. The findings from this study suggest that at least some structural changes detectable with OCT may occur in the long-term use of adalimumab in patients with ankylosing spondylitis. However, whether such changes translate into functional impairment remains to be elucidated in future studies with better controlled designs, probably including a large number of patients with a range of rheumatological diseases.

## AUTHORS' CONTRIBUTIONS

**NCY:** Conceptualization, Writing – original draft, Writing – review & editing. **MAO, IFS:** Data curation, Formal analysis, Writing – review & editing. **SK:** Data curation, Writing – review & editing. **ST, HO:** Writing – review & editing.

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