Impact of Uveitis on Quality of Life: A Prospective Study from a Tertiary Referral Rheumatology-Ophthalmology Collaborative Uveitis Center in Italy

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ABSTRACT: **Background:** Non-infectious uveitis (NIU) leads to severe visual impairment, potentially impacting on health-related quality of life (QoL).

Objectives: To investigate the impact of NIU on QoL.

Methods: Eighty NIU patients and 23 healthy controls completed the 36-item Short-Form Health Survey (SF)-36. The SF-36 values were statistically analyzed to evaluate differences between patients and healthy controls and to identify correlations between SF-36 subscores and clinical/demographic data.

Results: NIU patients showed a decrease in the physical component summary score ($P < 0.0001$) compared to healthy controls, while no difference was highlighted in the mental component summary score ($P = 0.97$). NIU patients showed a decrease in physical functioning ($P = 0.008$), role-physical ($P = 0.003$), bodily pain ($P = 0.0001$), general health ($P < 0.0001$), and social functioning ($P = 0.01$). Physical functioning was lower in patients with acute anterior uveitis (AAU) than in those with panuveitis ($P = 0.003$). No differences were found between patients with bilateral or unilateral NIU, isolated NIU, or NIU associated with systemic diseases and with or without ocular activity. No correlations were identified between best-corrected visual acuity and SF-36 subscores. Physical functioning ($P = 0.02$), bodily pain ($P = 0.004$), and social functioning ($P = 0.02$) were reduced in males versus females.

Conclusions: QoL is impaired in individuals with NIU, particularly in the physical domains, general health, and social functioning. AAU affects physical functioning more than panuveitis. NIU seems to affect per se QoL disregarding inflammatory activity, visual impairment, and presence of associated systemic diseases.

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KEY WORDS: non-infectious uveitis (NIU), quality of life, SF-36 questionnaire, anterior uveitis, panuveitis

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Non-infectious uveitis (NIU) is an inflammatory condition representing a major cause of visual impairment among the working-age population [1]. It may involve either a single eye or be bilateral, and can occur as an outlying isolated manifestation or in the context of an immune-mediated systemic inflammatory condition such as spondyloarthritis, Behçet's disease, sarcoidosis, Vogt-Koyanagi-Harada disease, and multiple sclerosis [2]. Inflammation may affect both the uveal tract (composed by the iris, choroid, and ciliary body) and the adjacent structures (including the sclera, retina, and optic nerve). In particular, the involvement of the anterior chamber results in anterior uveitis, while posterior uveitis affects the retina or choroid. Intermediate uveitis is a form of uveitis localized to the vitreous and peripheral retina. The term panuveitis is used when inflammation is observed in the anterior chamber, vitreous, and retina and/or choroid with no predominant site of disease. Retinal vasculitis is a retinal vascular change accompanying ocular inflammation and consisting in perivascular sheathing and vascular leakage or occlusion on fluorescein angiogram [3]. Uveitic macular edema (UME), which is the main condition associated with vision impairment in uveitis, is a structural complication occurring in up to 65% of intermediate uveitis and panuveitis. In addition, UME may persist long after the resolution of ocular inflammation and even when active uveitis is effectively controlled by treatment [4,5]. Despite the increasing number of treatment choices [6-8], uveitis may lead to severe visual impairment and several ocular complications including glaucoma, cataract, optic nerve damage, and retinal lesions [9], thus potentially reducing the health-related quality of life (QoL) standards as shown in several studies [10-13]. Moreover, NIU is particularly prevalent in young and the working-age population, further amplifying its economic and social impact [14]. Our study aimed to investigate the impact of NIU on QoL in a cohort of Italian patients by

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using the Short-Form (SF)-36 QoL scale, a questionnaire validated for the Italian population and widely used for evaluating QoL in ocular diseases [11-13,15,16].

PATIENTS AND METHODS

Eighty consecutive Italian patients with NIU attending the Tertiary Referral Rheumatology-Ophthalmology Collaborative Uveitis Outpatients Clinic from the 1 January 2016 to 29 February 2016 prospectively completed the SF-36 QoL questionnaire to assess their QoL. The SF-36 was also administered to 23 Italian healthy controls during the same time period.

Two SF-36 summary scores were evaluated: the physical component summary (PCS) score and the mental component summary (MCS) score. In addition, the following eight subscales of the SF-36 were investigated: physical functioning, social functioning, role-physical, role-emotional, mental health, vitality, bodily pain, and general health. The two summary scores and each subscale range from 0 to 100, with 0 and 100 being the worst and best QoL score, respectively. Patients and healthy controls were asked to compile all SF-36 questions taking into account only the preceding 4 weeks [16]. All subjects completed the SF-36 form in different moments of disease activity, as attested by a complete ophthalmologic evaluation, and NIU was classified according to the Standardization of Uveitis Nomenclature (SUN) working group criteria [3]. Both the ophthalmological and the rheumatologic visits were performed on the same day.

Diagnosis of psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V and dependence on alcohol or other substances were considered exclusion criteria.

The primary aim of our study was to evaluate QoL in patients with NIU compared to healthy controls. The secondary aims of the study were to:

- Identify differences in QoL between patients with acute anterior uveitis (AAU), panuveitis and posterior uveitis
- Evaluate any correlation between age, age at disease onset, disease duration, and gender
- Investigate differences in patients with unilateral and bilateral ocular involvement
- Identify differences in patients with and without retinal vasculitis
- Correlate QoL impairment with the presence of UME
- Correlate QoL impairment with best-corrected visual acuity (BCVA) evaluated with the Snellen scale in decimal fractions
- Disclose any correlation between QoL impairment and uveitis activity at the time of SF-36 completion and during the preceding 12 months.

Our primary endpoint was represented by the assessment of any statistically significant difference between NIU patients and healthy controls in the SF-36 QoL summary scores and each SF-36 subscore. Our secondary endpoints were represented by the assessment of any statistically significant difference in the SF-36 QoL summary scores and in each SF-36 subscore in:

- Patients with AAU and patients with panuveitis
- Patients with and without active ocular inflammation at the time of the SF-36 questionnaire completion as well as during the preceding 12 months, according to the SUN criteria [3]
- Patients with and without active retinal vasculitis at fluorescein angiography (FA).

We also assessed differences between male and female patients. Further secondary endpoints were represented by a correlation coefficient of at least 0.3 at statistical analysis between SF-36 QoL summary scores or each SF-36 subscore and age, age at NIU onset, disease duration, BCVA, and central macular thickness (CMT) measured by optical coherence tomography (OCT).

Descriptive statistics were used for sample size, percentages, means, and standard deviations. After evaluating normality of data with the Anderson–Darling test, we used the Mann–Whitney U test or unpaired Student's *t*-test for pairwise comparisons and Pearson's test or Spearman's test for correlations according to data distribution. GraphPad Prism 6.0 software Graphpad Prism 6.0 software (GraphPad Software Inc, USA) was used for statistical analysis. Significance was defined as $P < 0.05$. Because of the small number of patients with posterior uveitis, no comparisons were made between posterior uveitis and AAU or panuveitis. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of Azienda Ospedaliera Universitaria Senese (University of Siena, Siena, Italy). Informed consent was obtained from all participants.

RESULTS

Eighty (40 males, 40 females) consecutive Caucasian Italian patients with NIU were prospectively enrolled in our study. The mean age of the patients was 45.65 ± 12.53 years; the mean age at NIU onset was 35.41 ± 12.32 years with a mean NIU duration of 10.21 ± 12.32 years. Thirty-one patients (38.75%) had AAU, 2 (2.5%) intermediate uveitis, 8 (10%) posterior uveitis, and 39 (48.75%) panuveitis. Retinal vasculitis was identified in 8 (10%) cases. Ocular involvement was unilateral in 41 (51.2%) patients and bilateral in 39 (48.8%) cases. NIU occurred in the context of an immune-mediated systemic inflammatory condition in 53 (66.3%) cases. Thirty-one (38.8%) patients had presented at least one ocular inflammatory flare during the 12 months preceding the SF-36 completion; more specifically, 13/31 (41.9%) patients with AAU and 16/39 (41%) patients with panuveitis experienced at least one ocular inflammatory flare during the preceding 12 months.

Table 1. Clinical and therapeutic data from patients enrolled in the study. Biologic agents include both tumor necrosis factor and interleukin-1 inhibitors

	N (%)	Oral corticosteroids, n (%)	DMARDs, n (%)	Biologic Agents, n (%)
Location of uveitis				
Anterior	31 (38.8)	11 (35.5)	10 (32.3)	10 (32.3)
Intermediate	2 (2.5)	0 (0)	2 (100)	2 (100)
Posterior	8 (10)	5 (62.5)	3 (37.5)	0 (0)
Panuveitis	39 (48.8)	37 (94.9)	23 (59)	20 (51.3)
Systemic diagnosis				
Idiopathic uveitis	27 (33.8)	4 (14.8)	2 (7.4)	1 (3.7)
Behçet's disease	45 (56.3)	45 (100)	34 (75.6)	26 (57.8)
Ankylosing spondylitis	5 (6.3)	2 (40)	0 (0)	3 (60)
Psoriasic arthritis	2 (2.5)	2 (100)	2 (100)	1 (50)
Vogt Koyanagi Harada disease	1 (1.3)	0 (0)	0 (0)	1 (100)
Additional eye information				
Retinal vasculitis	8 (10)	6 (75)	6 (75)	6 (75)
Monolateral involvement	41 (51.2)	22 (53.7)	12 (29.3)	10 (24.4)
Bilateral involvement	39 (48.8)	31 (79.5)	26 (66.7)	22 (56.4)
Patients with ocular flares at SF-36 fulfillment	16 (20)	11 (68.8)	9 (56.3)	5 (31.3)
Patients with ocular flares during the previous 12 months	31 (38.8)	18 (58)	15 (48.4)	10 (32.3)

DMARDs = disease modifying anti-rheumatic drugs, SF-36 = 36-item Short-Form Health Survey

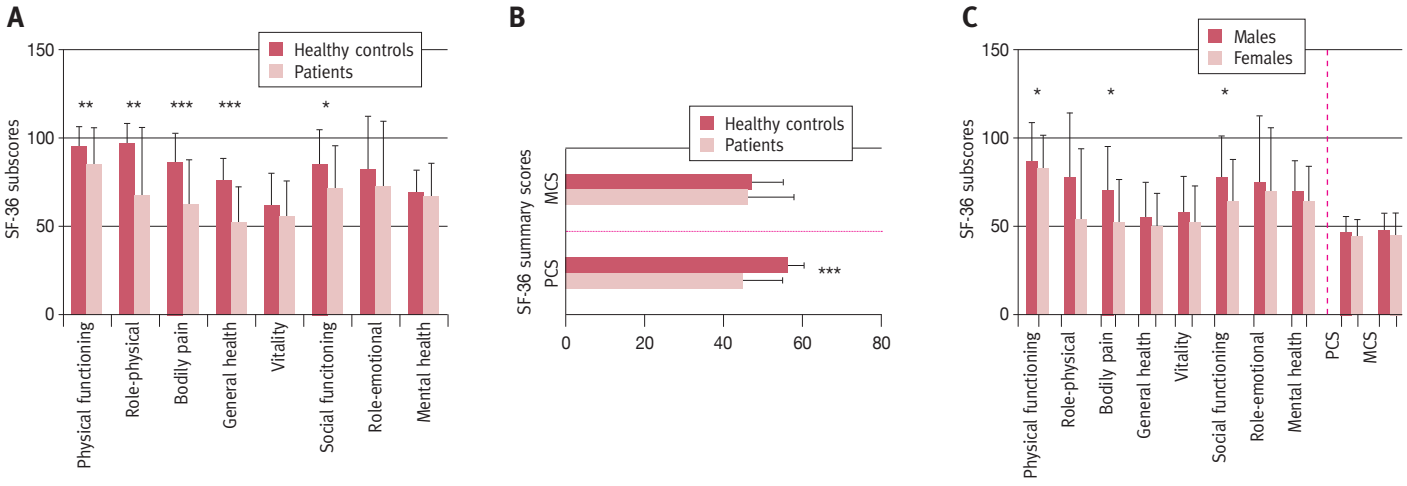
At the time of SF-36 questionnaire completion, 38 patients (47.5%) were under disease modifying anti-rheumatic drugs (DMARDs) treatment, 32 (40%) were under anti-tumor necrosis factor (TNF)-α or anti-interleukin (IL)-1 biologic agent therapy. Oral corticosteroids were given to 53 (66.3%) patients. Table 1 summarizes clinical and therapeutic information from patients enrolled. BCVA in the patients enrolled was 8.8 ± 2.7 (range 0-10) in the left eye and 8.8 ± 2.9 (range 0–10) in the right eye. Central macular thickness measured by OCT was 275.6 ± 56.5 µm (range 210–593) in the left eye and 265.4 ± 46.03 µm (range 116–414) in the right eye.

When evaluating any difference in the SF-36 summary scores between NIU patients and healthy controls, the former showed a significant decrease in PCS ($P < 0.0001$), while no statistically significant difference was highlighted with regard to MCS ($P = 0.97$). More specifically, looking at the different SF-36 subscores, NIU patients showed a significant decrease in the physical functioning ($P = 0.008$), role-physical ($P = 0.003$), bodily pain ($P = 0.0001$), general health ($P < 0.0001$), and social functioning ($P = 0.01$) domains, while no statistically significant differences were identified regarding vitality ($P = 0.23$), role-emotional ($P = 0.29$) and mental health ($P = 0.93$). Figure 1A and 1B graphically describes differences between NIU patients and healthy controls.

When comparing the SF-36 scores between patients with AAU and panuveitis, the former group showed a significant reduction in the physical functioning ($P = 0.003$) subscore, while no statistically significant differences were identified in relation to PCS ($P = 0.57$) or MCS ($P = 0.46$). No statistically significant differences were found between patients with bilateral and unilateral ocular involvement. Similarly, no significant differences were identified between patients with isolated uveitis and those affected by a concomitant immune-mediated systemic inflammatory condition (data not shown).

As summarized in Table 2, a weak inverse correlation was found between age and physical functioning ($\rho = -0.32$, $P = 0.03$), while no relevant correlations were found between SF-36 summary scores/subscores and age at NIU onset or disease duration. Conversely, physical functioning ($P = 0.02$), bodily pain ($P = 0.004$) and social functioning ($P = 0.02$) were sig-

Figure 1. Short Form (SF)-36 subscores **[A]** and summary scores **[B]** assessed in patients and healthy controls. Differences between male and female patients are also pointed out **[C]**



PCS = physical component summary, MCS = mental component summary
*P ‹ 0.05, **P ‹ 0.001, ***P ≤ 0.0001

Table 2. Rank correlation coefficients assessing the correlation between demographic, clinical or instrumental data and Short-Form 36 summary scores/subscores

		Physical functioning	Role-physical	Bodily pain	General health	Vitality	Social functioning	Role-emotional	Mental health	PCS	MCS
Age	Rho	-0.32	-0.20	-0.14	-0.15	0.05	-0.13	-0.18	0.1	-0.29	0.03
	P value	0.03	0.09	0.24	0.17	0.66	0.42	0.1	0.38	0.03	0.92
Age at onset	Rho	-0.09	-0.14	-0.06	-0.04	0.006	-0.17	-0.17	0.07	-0.12	-0.004
	P value	0.43	0.23	0.64	0.77	0.96	0.15	0.14	0.55	0.31	0.97
Disease duration	Rho	-0.23	-0.08	-0.1	-0.12	0.08	0.12	0.03	0.08	-0.23	0.13
	P value	0.05	0.48	0.39	0.31	0.52	0.33	0.82	0.4925	0.047	0.29
BCVA	Rho	-0.12	0.07	-0.02	0.04	-0.06	0.004	-0.14	-0.03	-0.004	-0.02
	P value	0.19	0.41	0.83	0.68	0.55	0.96	0.16	0.72	0.96	0.79
CMT	Rho	0.21	0.35	0.25	0.19	0.25	0.26	0.30	0.17	0.22	0.32
	P value	0.03	0.0002	0.009	0.054	0.009	0.006	0.002	0.09	0.02	0.0009

Coefficients were obtained with Spearman's or Pearson's test according to data distribution.
BCVA = best corrected visual acuity, CMT = central macular thickness, PCS = physical component summary, MCS = mental component summary

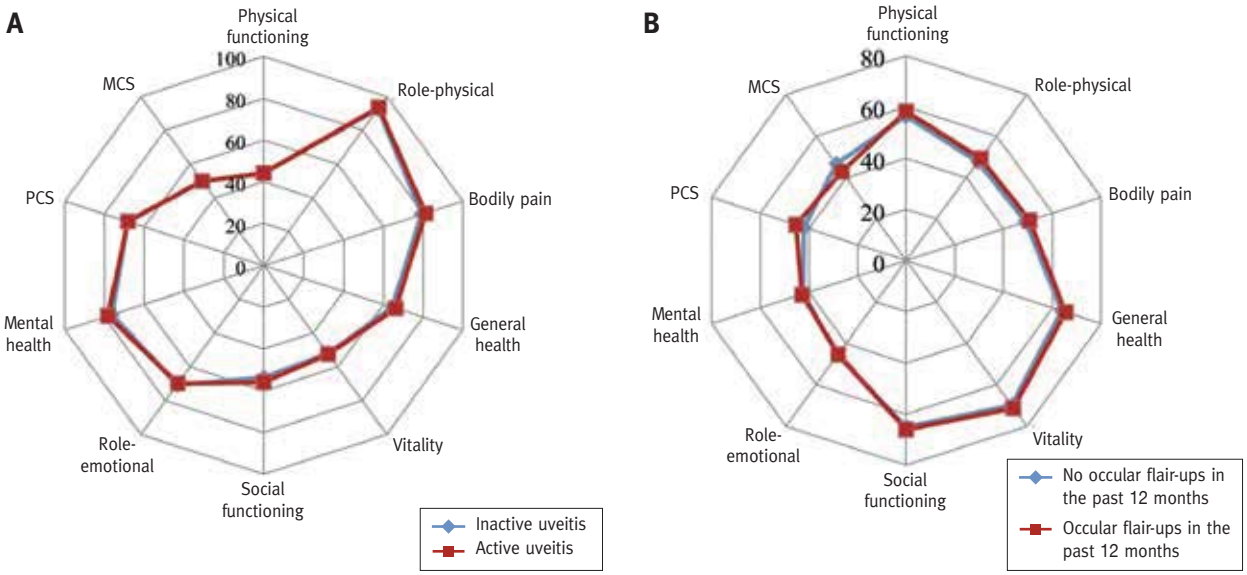
nificantly reduced in male compared to female patients, while no statistically significant differences were found in PCS (P = 0.10) and MCS (P = 0.44) with regard to gender. Figure 1C summarizes the differences identified between male and female NIU patients. No correlations were identified between BCVA values and any of SF-36 summary scores/subscores; conversely, a weak correlation was found between CMT and role-physical (ρ = 0.35, P = 0.0002), role-emotional (ρ = 0.30, P = 0.002) and MCS (ρ = 0.32, P = 0.0009). No statistically significant differences were identified according to the presence or absence of active retinal vasculitis.

As shown in Figure 2, no statistically significant differences were found in SF-36 summary scores and/or SF-36 subscores between patients with and without ocular inflammatory flares during the preceding 12 months as well as between patients with and without an ocular inflammatory flare at the time of the SF-36 questionnaire completion.

DISCUSSION

In our study we confirmed a meaningful reduction in QoL among patients suffering from NIU compared to healthy con-

Figure 2. Radar charts representing mean values of Short Form-36 QoL subscores and summary scores between **[A]** patients with and without active uveitis at the writing-out of the questionnaire and **[B]** patients with and without ocular inflammatory activity during the 12 months preceding the questionnaire completion. Notably, the two lines describing the two subgroups of patients are almost overlapping in both cases.



PCS = physical component summary, MCS = mental component summary

trols. In addition, we found that AAU affects QoL significantly more than panuveitis regarding physical functioning.

Along with our results, other studies have shown the impact of NIU on QoL. In particular, Maca and co-authors [10] found that AAU induced a reduction in mental and physical scores attested by an SF-8 health survey. Similarly, and consistently with what identified in the present study, AAU has been associated with physical health limitation on SF-36 scores in patients with recent inflammatory low-back pain suggestive of spondyloarthritis [11]. Notably, Hui et al. [12] found a significantly lower PCS and MCS in 60 patients with uveitis compared to healthy controls. Accordingly, Schiffman and colleagues [13] evaluated QoL in 76 patients with anterior, posterior, intermediate, or pan-uveitis and found that both PCS, MCS and all but bodily pain subscores were significantly affected in uveitis patients more than with age-matched healthy controls. As in our study, no differences in SF-36 scores were found among patients with unilateral or bilateral involvement; nevertheless, patients with posterior/pan-uveitis showed a poorer QoL in relation to bodily pain and general health than subjects with AAU. In the same way, role-physical, mental health, MCS, and PCS were significantly decreased in patients with active uveitis than in those with inactive ocular disease [13]. Compared to our results, both Hui et al. [12] and Schiffman et al. [13] found a larger number of statistically significant differences between patients with uveitis and healthy controls. In particular, we identified no significant differences regarding the mental domains between patients and healthy controls. In contrast to Schiffman et al., we found a more severe impact on QoL in patients with AAU compared with those with panuveitis. This finding is likely due to the fact that AAU is usually associated with a higher recurrence rate than panuveitis. Moreover, AAU is also the most painful form of NIU and therefore it may represent the most frightening form of NIU for patients, disregarding the more severe clinical impact of panuveitis in terms of ocular long-term complications. Patients with panuveitis are more frequently under treatment with systemic therapies, including corticosteroids and biologic agents, than patients with AAU who are more commonly treated with topical therapies. Consequently, the lower impact on physical functioning in patients with panuveitis may be somehow due to a tighter clinical and pharmaceutical management than AAU patients.

Moreover, these different results may be explained with the different cohort of patients enrolled. Our cohort of patients with posterior uveitis and panuveitis showed a very low rate of ocular complications and had a relatively preserved visual acuity. Indeed, almost all subjects with posterior and pan-uveitis enrolled in our study exhibited a BCVA greater than 8/10 in both eyes at the time of the SF-36 questionnaire completion.

The analysis of health-related QoL has also been performed on 224 patients participating to the HURON trial in the context of intermediate or posterior NIU [17]. In this case, a significantly lower mean score was identified for the role-emotional, mental health, role-physical, vitality, general health, and MCS [17]. However, since patients with AAU and panuveitis were not included, a direct comparison with our results is not possible.

The deterioration of QoL in our patients did not correlate with the presence of a concomitant associated systemic disease, unilateral or bilateral involvement, presence of retinal vasculitis, NIU duration, or age at NIU onset, while significant differences were identified between male and female patients, with the latter showing worse physical functioning as well as general health and role-emotional subscores. A weak correlation was found between age at SF-36 completion and physical functioning as well as between CMT values at OCT and role-physical, role-emotional and MCS. Interestingly, no differences were identified according to ocular inflammatory activity at the time of SF-36 questionnaire completion and during the preceding 12 months. Similarly, no correlation was identified between SF-36 summary scores/subscores and BCVA.

All together, our findings suggest that NIU affects per se the QoL of patients beyond disease activity and visual impairment. The impact of NIU on QoL might be likely due to its tendency to relapse (with a greater rate of recurrence in AAU than panuveitis), to the symptoms of uveitis such as pain in AAU that can be frightening and prostrating for the patients, to the need for a close follow-up, as well as to the concern for a possible vision impairment and development of ocular complications. In support of this finding, Onal et al. [18] observed that general health was more affected than visual functioning in patients with Behçet's disease-related uveitis and that many other factors were imputable in decline in QoL scores in patients.

CONCLUSIONS

In conclusion, our data show that QoL is meaningfully affected by NIU, especially in relation to physical domains, general health, and social functioning. Moreover, patients with AAU are more limited in their physical functioning than patients with panuveitis. Evaluating gender differences, females have shown to be significantly more impaired in physical and social functioning as well as bodily pain than males. In our patients, NIU impaired QoL despite a very low rate of ocular complications and independently from ocular inflammatory activity or the presence of a concomitant systemic disorder. Overall, our data suggest that other unrecognized factors, not necessarily ocular, may affect QoL in patients with NIU, including the relapsing disease course, the frightening symptoms and the concern for a possible vision impairment or development of ocular complications.

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Capsule

Tug of war with anti-PD-1

Antibodies against immune checkpoint proteins such as programmed cell death 1 (PD-1) are gaining increasing prominence in cancer treatment, but these promising therapeutics do not always work. To be effective in preventing T cells from becoming exhausted, antibodies against PD-1 must remain bound to the T cells. Arlauckas and colleagues discovered that although antibodies against PD-1 initially bound to T cells as intended, tumor-associated macrophages quickly removed the antibodies, thus inactivating them. In an encouraging finding, however, inhibiting Fcγ receptors prevented removal of antibodies against PD-1 and prolonged their effects in vivo.

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Eitan Israeli

Capsule

A heart–brain–kidney network controls adaptation to cardiac stress through tissue macrophage activation

Heart failure is a complex clinical syndrome characterized by insufficient cardiac function. In addition to abnormalities intrinsic to the heart, dysfunction of other organs and dysregulation of systemic factors greatly affect the development and consequences of heart failure. Fujiu et al. showed that the heart and kidneys function cooperatively in generating an adaptive response to cardiac pressure overload. In mice subjected to pressure overload in the heart, sympathetic nerve activation led to activation of renal collecting-duct (CD) epithelial cells. Cell–cell interactions among activated CD cells, tissue macrophages and endothelial cells within the kidney led to secretion of the cytokine CSF2, which in turn stimulated cardiac-resident Ly6C^{lo} macrophages, which are essential for the myocardial adaptive response to pressure overload. The renal response to cardiac pressure overload was disrupted by renal sympathetic denervation, adrenergic β2-receptor blockade or CD-cell-specific deficiency of the transcription factor KLF5. Moreover, the authors identified amphiregulin as an essential cardioprotective mediator produced by cardiac Ly6C^{lo} macrophages. These results demonstrate a dynamic interplay between the heart, brain, and kidneys that is necessary for adaptation to cardiac stress, and they highlight the homeostatic functions of tissue macrophages and the sympathetic nervous system.

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