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ORIGINAL ARTICLE

Impact of HLA-B51 on Uveitis and Retinal Vasculitis: Data from the AIDA International Network Registries on Ocular Inflammatory Disorders

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ABSTRACT

Purpose: The clinical relevance of human leukocyte antigen (HLA) subtypes such as HLA-B51 on Behçet's disease (BD)-related uveitis and non-infectious uveitis (NIU) unrelated to BD remains largely unknown.

Methods: Data were prospectively collected from the International AIDA Network Registry for BD and for NIU. We assessed differences between groups (NIU unrelated to BD and positive for HLA-B51, BD-related uveitis positive for HLA-B51 and BD-related uveitis negative for HLA-B51) in terms of long-term ocular complications, visual acuity (VA) measured by best corrected visual acuity (BCVA), anatomical pattern, occurrence of retinal vasculitis (RV) and macular edema over time.

Results: Records of 213 patients (341 eyes) were analyzed. No differences in complications were observed ($p = 0.465$). With regard to VA, a significant difference was detected in median BCVA ($p = 0.046$), which was not maintained after Bonferroni correction ($p = 0.060$). RV was significantly more prevalent in NIU-affected patients who tested positive for HLA-B51, irrespective of the systemic diagnosis of BD ($p = 0.025$). No differences emerged in the occurrence of macular edema ($p = 0.99$).

Conclusions: Patients with NIU testing positive for HLA-B51 exhibit an increased likelihood of RV throughout disease course, irrespective of a systemic diagnosis of BD. The rate of complications as well as VA are comparable between NIU cases unrelated to BD testing positive for HLA-B51 and uveitis associated with BD. Therefore, it is advisable to perform the HLA-B typing in patients with NIU or retinal vasculitis, even in the absence of typical BD features.

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Uveitis represents a preventable cause of blindness worldwide that impacts patients' quality of life in several domains beyond mere visual acuity, thus carrying a high socioeconomic burden.[1,2] Long-standing, uncontrolled intraocular inflammation is associated with a high risk of developing irreversible complications that ultimately lead to a poor visual outcome.[3,4] The detailed pathogenetic mechanisms underlying Non-Infectious (NIU) Uveitis are yet to be fully elucidated. However, increasing evidence over time has suggested a central role of specific human leukocyte antigens in the immune response and in the increased susceptibility to develop potentially blinding forms of uveitis. For instance, human leukocyte antigen (HLA)-B27 and HLA-B51 markedly increase the likelihood of developing acute anterior uveitis and Behçet's disease (BD).[5] Since the first description in 1982 associating HLA-B51 with a higher risk of developing BD,[6] other studies including genome-wide association studies as well as meta-analysis have investigated this topic and confirmed the association.[7–9] Interestingly, HLA-B51 has been hypothesized to increase the risk of developing ankylosing spondylitis, psoriatic arthritis (PsA) and ocular-specific entities, although with a low degree of evidence.[10–12] Moreover, HLA-B5 was also found to be significantly more present among patients affected by NIU.[13]

From a clinical standpoint, it appears that the HLA-B51 positivity influences the disease phenotype in patients with BD. Specifically, patients testing positive for HLA-B51 are more likely to experience ocular involvement[14–16] while gastrointestinal and neurologic involvement are more prominent in certain populations.[17] Nonetheless, the exact clinical relevance of HLA-B51 in ocular BD and other conditions such as idiopathic NIU remains a mystery.

We herein provide a comprehensive analysis of the impact of HLA-B51 in BD uveitis and NIU unrelated to BD from patients enrolled in the international AIDA registry, with a particular focus on differences between these groups.

Materials and methods

Study design and participants

Medical records of patients affected by BD enrolled in the AIDA registry were reviewed.[18] Patients affected by NIU testing positive for HLA-B51 who did not exhibit any signs of BD were also enrolled.[19] The following demographic, clinical, and therapeutic data were collected: age, sex, age at disease onset, disease duration, ocular complications, best corrected visual acuity (BCVA) measured on Snellen charts and expressed in decimals, retinal vasculitis, macular edema, and treatment courses. BD was diagnosed according to the International Study Group (ISG) criteria and/or International Criteria for Behçet's Disease (ICBD) criteria.[20,21] Uveitis was classified according to the Standardization of Uveitis Nomenclature criteria.[22] All patients were systematically followed-up every 3-to-6 months and in case of necessity (disease flare and/or safety issues). Incomplete records with more than 20% missing values were excluded from the study. Patients testing positive for HLA-B27 were also excluded. NIU was defined as uveitis of non-infectious etiology unrelated to BD or to any specific ocular inflammatory entity.

Aims and endpoints

The primary aim of the study was to assess the impact of HLA-B51 on long-term ocular outcomes of BD-related uveitis and NIU unrelated to BD with a particular focus on potential differences between the following three subgroups: NIU unrelated to BD positive for HLA-B51, BD-related uveitis positive for HLA-B51, and BD-related uveitis negative for HLA-B51. Secondary aims were to: (i) assess any differences in the anatomical pattern between groups; (ii) explore its influence on retinal vasculitis; (iii) estimate the effect of HLA-B51 on macular edema by differentiating between the groups.

The primary endpoint was evaluated by potential statistically significant differences between BD-related uveitis positive for HLA-B51, BD-related uveitis negative for HLA-B51 and NIU unrelated to BD, positive for HLA-B51 in terms of long-term complications and BCVA assessed at last follow-up. Secondary aims were examined by any statistically significant differences in the anatomical pattern and occurrence rate over time of retinal vasculitis and cystoid macular edema between the three groups.

Subsequently, a subanalysis was performed after excluding all patients with a systemic immune-mediated disease from the NIU group and the three subgroups were compared with the same endpoints as previously listed.

Protocol approval and ethical statement

The study conformed to the tenets of the Declaration of Helsinki and received approval by the local Ethics Committee of the University of Siena (Reference No. 14951). Informed consent was obtained from all patients or their legal guardians.

Statistical analysis

Statistical analysis was performed using IBMSPSS Statistics for Windows, version 28 (IBM Corp., Armonk, NY, United States). Descriptive statistics was employed to display mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Shapiro–Wilk test was used to assess the normality of our data. Cross-tables were analyzed by Pearson's chi-square test and *post-hoc* test with adjusted residuals in case of contingency tables with dimensions greater than 2×2. Potential differences in mean on multiple comparisons were assessed by Kruskal-Wallis H followed by Mann-Whitney U test for *post-hoc* analysis. Bonferroni correction was subsequently applied. The threshold for statistical significance was set to $p < 0.05$, and all p-values were two-sided.

Results

Overall, 213 patients were enrolled in the study with a male-to-female ratio of 1.57/1, for a total of 341 eyes. Figure 1 shows the selection process of the cohort taken into examination. Ocular involvement was bilateral in 66, 43 and 19 patients with BD-related uveitis positive for HLA-B51, BD-related uveitis negative for HLA-B51 and NIU unrelated to BD, positive for HLA-B51, respectively. The mean age of the entire cohort was 32.18 ± 15.52 years. Figure 2 illustrates the distribution across age groups for the three groups. Demographic, clinical and therapeutic characteristics for each group are provided in Table 1.

All three groups exhibited roughly similar demographic and therapeutic characteristics. Specifically, no differences were observed in terms of age at onset ($p = 0.945$) and laterality ($p = 0.627$). With regard to systemic treatment with advanced therapies, patients with NIU positive for HLA-B51 received biologic agents in 38.7% of cases while BD patients affected by uveitis positive for HLA-B51 and negative for HLA-B51 were treated with biologic agents in 56.2% and 50.6%, respectively ($p = 0.67$). On the other hand, we observed an overall significant treatment delay ($p = 0.044$) with a tendency of higher mean delay among BD patients with uveitis negative for HLA-B51 which did not preserve the statistical significance after Bonferroni correction ($p = 0.06$ and $p = 0.069$).

No differences in terms of complications were observed between groups ($p = 0.465$). More in detail, 101 complications in 56 out of 171 eyes (32.7%) were recorded for BD-related uveitis positive for HLA-B51, 60 complications in 31 out of 120 eyes (25.8%) were recorded for BD-related uveitis negative for HLA-B51 and 22 complications in 12 out of 50 eyes (24.0%) were observed in patients with NIU who tested positive for HLA-B51. The most frequent complications detected in the entire cohort (341 eyes) were represented by cataract ($n = 42$, 12.31%), followed by macular edema ($n = 38$, 11.1%), epiretinal membranes ($n = 12$, 3.5%), posterior synechiae ($n = 11$, 3.2%), optic nerve atrophy ($n = 9$, 2.6%), retinal detachment ($n = 9$, 2.6%), ocular hypertension or glaucoma ($n = 7$, 2.1%) and peripheral anterior synechiae ($n = 7$, 2.1%). Figure 3 illustrates all complications for each group of patients.

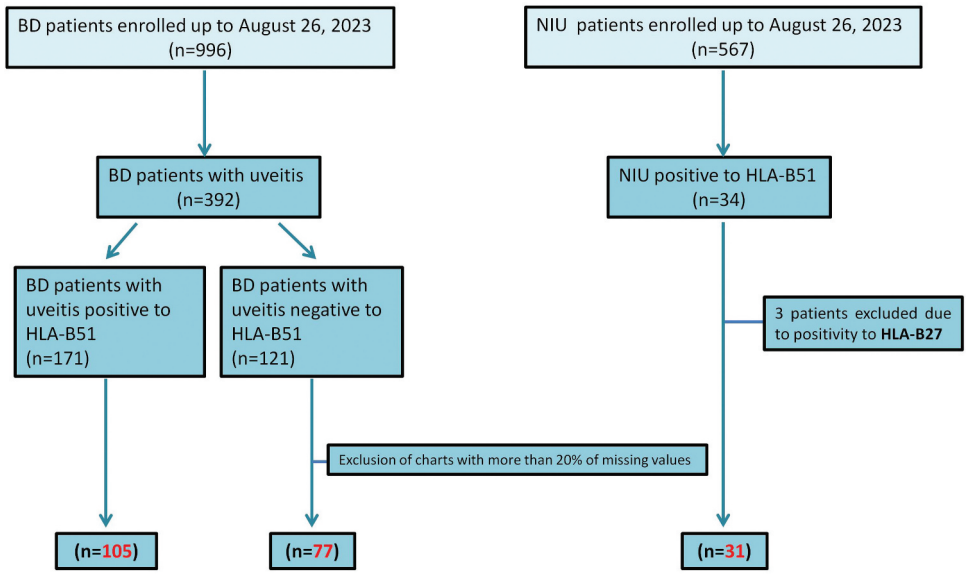

Figure 1. Chart showing the selection process for the cohort examined. List of abbreviations: BD Behçet's disease, HLA human leukocyte antigen, NIU non-infectious uveitis.

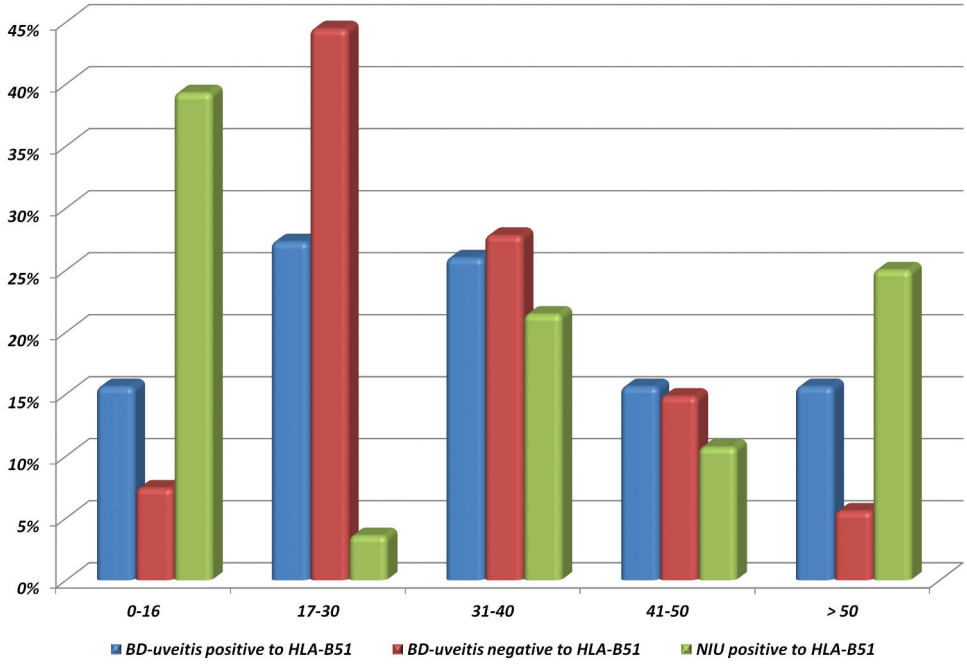

Figure 2. Distribution of age at onset for each group separated for different age groups, expressed in years. List of abbreviations: *BD* Behçet's disease, *HLA* human leukocyte antigen.

Concerning visual acuity, an overall significant difference was detected in median BCVA ($p = 0.046$) which did not maintain statistical significance after Bonferroni correction during *post-hoc* analysis of pair comparisons ($p = 0.060$). Median (IQR) BCVA for NIU positive for HLA-B51, BD-related uveitis positive for HLA-B51 and BD-related uveitis negative for HLA-B51 was 1.00 (0.10), 1.00 (0.20) and 1.00 (0.30), respectively.

Regarding the anatomical pattern, anterior uveitis was significantly more represented among patients with NIU patients who tested positive for HLA-B51 ($p < 0.001$).

Retinal vasculitis was significantly less prevalent among patients affected by BD-related uveitis who tested negative for HLA-B51 ($p = 0.025$). Retinal vasculitis was present in 10 out of 50 eyes (20.0%) among patients with NIU positive for HLA-B51, in 37 out of 164 eyes (22.6%) in BD patients positive for HLA-B51 and in 12 out of 117 eyes (10.3%) in BD patients negative for HLA-B51. On the contrary, no differences emerged between groups in the occurrence rate of macular edema ($p = 0.99$).

A subanalysis was performed after excluding patients with a systemic diagnosis in the NIU group unrelated to BD. No

Table 1. Lists demographic, clinical and therapeutic data for each of the 3 groups.

	NIU positive for HLA-B51	BD-uveitis positive for HLA-B51	BD-uveitis negative for HLA-B51
n of patients	31	105	77
Mean ± SD age at onset (years)	32.36 ± 23.10	32.67 ± 14.93	31.36 ± 11.21
Mean ± SD disease duration (years)	7.15 ± 11.00	14.69 ± 10.53	16.36 ± 11.29
Mean ± SD follow-up (years)	6.26 ± 9.33	10.20 ± 4.09	10.92 ± 2.71
Male/Female	16/15	60/45	44/33
Laterality	Monolateral (*n* = 12) Bilateral (*n* = 19)	Monolateral (*n* = 39) Bilateral (*n* = 66)	Monolateral (*n* = 34) Bilateral (*n* = 43)
Anatomical Pattern* (*n* of eyes, %)	AU (*n* = 25, 50.0%) IU (*n* = 2, 4.0%) PU (*n* = 4, 8.0%) PaU (*n* = 18, 36.0%)	AU (*n* = 41, 24.0%) IU (*n* = 6, 3.5%) PU (*n* = 38, 22.2%) PaU (*n* = 86, 50.3%)	AU (*n* = 24, 20.0%) IU (*n* = 4, 3.3%) PU (*n* = 20, 16.7%) PaU (*n* = 72, 60.0%)
Associated systemic disease (*n* of patients, %)	SpA (*n* = 4, 12.9%) JIA (*n* = 3, 9.7%) PsA (*n* = 1, 3.2%) MS (*n* = 1, 3.2%) Idiopathic (*n* = 22, 71.0%)		
Treatment with biologic agents	ADA (*n*=12)	ADA (*n* = 36) IFX (*n* = 12) GOL (*n* = 4) CZP (*n* = 2) TCZ (*n* = 2) CAN (*n* = 1) ANA (*n* = 1) RTX (*n* = 1)	ADA (*n* =16) IFX (*n* = 16) GOL (*n* = 3) TCZ (*n* = 1) CAN (*n* = 1) ANA (*n* = 1) SCK (*n* = 1)
Treatment with cDMARDs	AZA (*n* = 1) MTX (*n* = 1) CsA (*n* = 2) SZS (*n* = 1)	AZA (*n* = 17) MTX (*n* = 5) CsA (*n* = 3) SZS (*n* = 3) CYC (*n* = 1) MFM (*n* = 1) HCQ (*n* = 2)	AZA (*n* = 13) CsA (*n* = 4) SZS (*n* = 1) CYC (*n* = 2) MFM (*n* = 1) HCQ (*n* = 1)

List of abbreviations: ADA adalimumab, ANA anakinra, AU anterior uveitis, AZA azathioprine, CAN canakinumab, cDMARDs conventional disease modifying anti-rheumatic drugs, CsA cyclosporine A, CYC cyclophosphamide, CZP certolizumab pegol, GOL golimumab, HCQ hydroxychloroquine, IFX infliximab, IU intermediate uveitis, JIA juvenile idiopathic arthritis, MFM mycophenolate mofetil, MS multiple sclerosis, MTX methotrexate, *n* number, PaU panuveitis, PsA psoriatic arthritis, PU posterior uveitis, RTX rituximab, SpA spondyloarthritis, SD standard deviation, SZS sulfasalazine, TCZ tocilizumab.

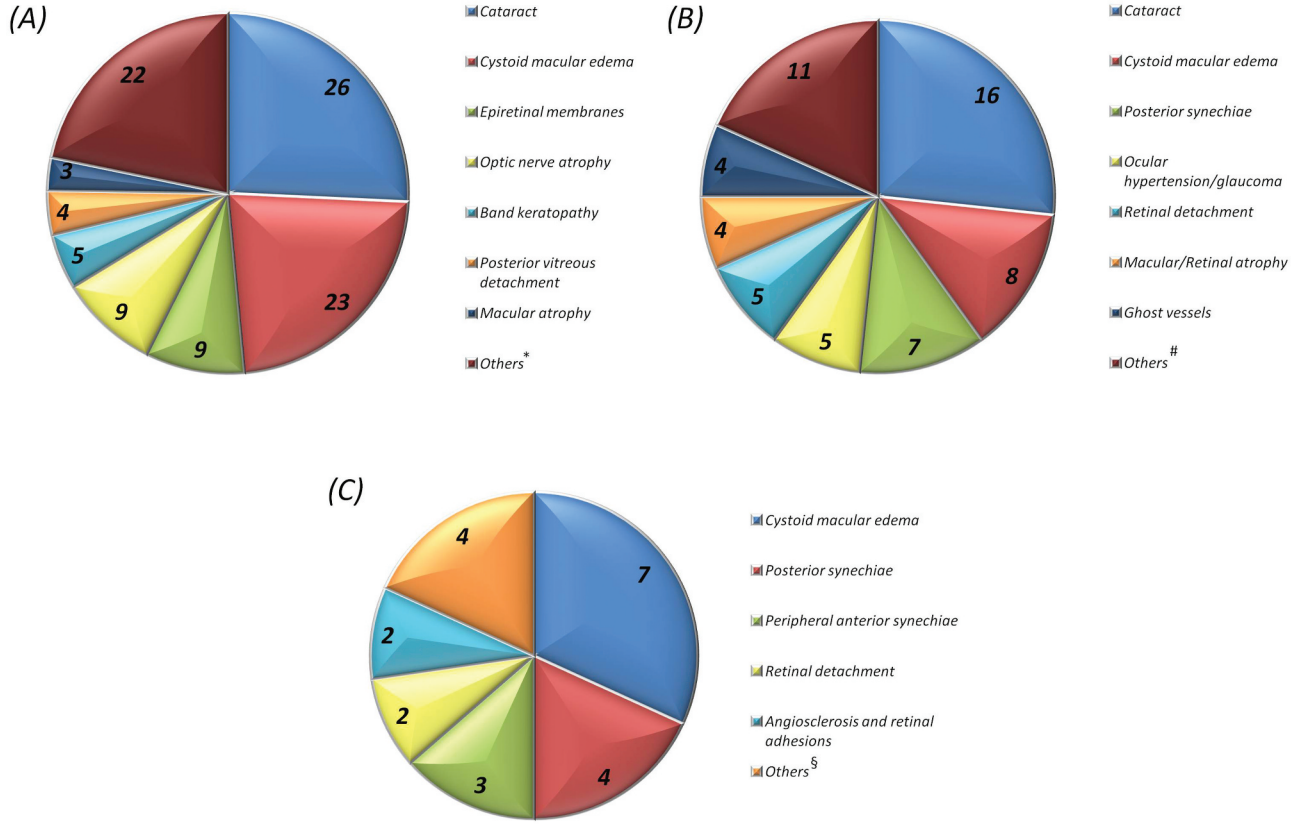

Figure 3. Complications for Behçet's disease (BD)-related uveitis positive for human leukocyte antigen (HLA)-B51 (A), BD-related uveitis negative for HLA-B51 (B), BD-unrelated non-infectious uveitis positive for HLA-B51 (C). * Pigmentation of the anterior capsular bag (*n* = 3), peripheral anterior synechiae (*n* = 2), ocular hypertension (*n* = 2), retinal ischemia (*n* = 2), retinal pigment epithelial alteration (*n* = 2), retinal scars (*n* = 2), retinal detachment (*n* = 2), phthisis bulbi (*n* = 2), exodeviated bulb (*n* = 1), retinoschisis (*n* = 1), vitreomacular traction (*n* = 1), pupillary seclusion (*n* = 1), ghost vessels (*n* = 1). # epiretinal membranes (*n* = 3), peripheral anterior synechiae (*n* = 2), retinal ischemia (*n* = 2), optic nerve atrophy (*n* = 1), macular ischemia (*n* = 1), pupillary seclusion (*n* = 1), iris bombè (*n* = 1). § Vitreomacular traction (*n* = 1), papillitis (*n* = 1), phthisis bulbi (*n* = 1), retinal scars (*n* = 1).

differences were observed in terms of long-term ocular complications, BCVA and CME ($p = 0.746$, $p = 0.076$, $p = 0.914$, respectively). Similarly, no differences with regard to the anatomical pattern were detected ($p > 0.05$). The significant difference in the RV occurrence rate persisted, with a significantly lower prevalence of RV in BD-related uveitis who tested negative for HLA-B51 ($p = 0.012$).

Discussion

Genetic background plays a major role in uveitis development. In this regard, specific HLA subtypes are closely associated with the development of sight-threatening forms of uveitis.[23–25]

In the current study, we investigated the influence of HLA-B51 on NIU and subsequently compared it with uveitis related to BD, whether positive or negative for HLA-B51. Long-term structural complications displayed no statistical differences among the three groups, indicating that the presence of HLA-B51 could significantly influence the long-term visual outcomes, irrespective of the systemic diagnosis. Notably, the incidence of long-term structural complications and visual acuity demonstrated similarities between NIU unrelated to BD but positive for HLA-B51 and BD-related uveitis. The latter is known for its dreadful effects on visual prognosis, particularly in untreated patients.[26,27] Therefore, individuals with NIU who test positive for HLA-B51 may be regarded as being at a comparable risk as patients with BD-related uveitis.

Macular edema emerged as one of the most common complications overall. It represents the most common cause of visual impairment in patients with uveitis and contributes to a worse prognosis. Undoubtedly, persistent intraretinal edema can result in cystic degeneration and photoreceptor damage, resulting in permanent central vision loss.[3]

Concerning visual acuity, there was no significant difference in mean BCVA among the groups. The propensity for a longer treatment delay in our BD-uveitis patients testing negative for HLA-B51 could also be responsible for the lack of differences observed between the 2 BD subgroups. Early aggressive treatment is potentially able to alter disease course and reduce the overall occurrence of irreversible long-term complications thus leading to a better visual outcome. In this context, we hypothesize that the absence of HLA-B51 may delay referral to specialized centers.

Interestingly, BD-uveitis patients negative for HLA-B51 were significantly less prone to develop retinal vasculitis during the disease course. In fact, the occurrence of retinal vasculitis in this subgroup was approximately half as frequent as in the other groups. It appears that the presence of HLA-B51 may exert a direct impact on the development of retinal vasculitis. This difference persisted also after the exclusion from the analysis of patients affected by systemic immune-mediated diseases.

However, it is important to highlight that qualitative differences between the groups were not assessed. BD-related retinal vasculitis is known to present as an occlusive retinal vasculitis and capillaritis.[27,28] On the other hand, retinal vasculitis in non-BD patients who tested positive for HLA-51 may exhibit distinct features with potentially different prognostic value.

These findings strongly support a serious ocular disease progression in individuals who test positive for HLA-B51, regardless of the concomitant systemic disease. More extensively, the comparable occurrence of long-term structural complications such as cataract, macular edema, epiretinal membranes, posterior synechiae, optic nerve atrophy, retinal detachment etc. alongside a higher risk of experiencing episodes of retinal vasculitis support to the notion of a generally unfavorable progression of ocular inflammatory disease in NIU patients who are positive for HLA-B51. In this regard, HLA-B51 has been identified as an independent predictor of developing complications in BD-related uveitis in a monocentric Italian cohort.[4] In support of this notion, Ohno and colleagues found a significantly higher frequency of visual acuity of 0.01 or less among female patients with HLA-B51.[6] Other studies have found an increased risk of ocular involvement in BD patients carrying the HLA-B51,[15,16] particularly posterior uveitis and visual impairment.[14] The presence of HLA-B51 may, in fact, shape the clinical picture and associate with a more frequent major organ involvement, particularly ocular disease. Whether a similar tendency in shaping the clinical presentation happens in the case of non-BD-related uveitis, is yet to be confirmed.

For this purpose, upcoming tailored studies should examine the impact of HLA-B51 on disease phenotypes. This includes identifying whether specific ocular characteristics in NIU tend to co-occur or cluster together.

Class I, HLA-B5, and its subclass B51 allele have the strongest association with BD, but its role in NIU is currently unknown. Nonetheless, one study found HLA-B5 to be significantly higher in patients with idiopathic uveitis and BD, suggesting a possible causative role of this haplotype in non-infectious intraocular inflammation.[13] Anecdotal evidence has suggested a pivotal role of this HLA allele in aseptic subconjunctival abscess as well as in idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome.[12,29] Small case series have also hypothesized a possible association between HLA-B51 positivity and SpA or PsA.[10,11] From a pathogenetic perspective, HLA-B51 may be responsible for a high intrinsic activation of neutrophils in BD patients.[30] Additionally, HLA class I molecules are critical for natural killer (NK) cells to distinguish between self and non-self and their interaction is mediated by killer cell Ig-like receptor (KIR). These interactions may explain part of the immune tolerance disruption in NIU.[31]

Altogether, our findings suggest a tight follow-up schedule in uveitis patients, especially when carrying the HLA-B51 allele, with the aim to prevent the development of irreversible ocular damage and the occurrence of frequent inflammatory attacks. In our cohort, approximately 55% of patients with NIU and 84% of BD patients have been treated with biologic agents (mainly anti-TNF-α agents) or cDMARDs. To this end, real-life multicenter experiences from tertiary referral centers have disclosed excellent results in the management of uveitis, either idiopathic or in the context of a systemic immune-mediated disorder with biologic agents, mainly TNF-α blockers, but also IL-1 inhibitors.[32–34]

Despite its international registry-based nature providing solid real-life data, some limitations should be acknowledged. First, it was not feasible to provide a detailed description of the

specific characteristics of retinal vasculitis, within this cohort, such as the involvement of venous or arterial retinal vasculature, whether it affected the posterior pole or peripheral retina, its propensity for necrotizing occlusion, or the occurrence of secondary ischemia and/or neovascularization. These details were outside the scope of the present study. Nevertheless, these initial findings suggest that a future investigation focusing on these specific aspects may be warranted to gain further insights into this issue. Secondly, detailed therapeutic data including treatment duration and/or endpoints related to response to treatment were not retrieved as it was not the main goal of the study. Therefore, the true impact of several and often sequential treatments was not assessed. Thirdly, regardless of the strength in the sheer volume of data of a registry-based study, a variable quality of collected data alongside the different clinical approach for each specific center may limit the availability of certain variables such as the timing of HLA-B typing and the basis of its testing, thus undermining the analysis of specific aims. Lastly, it is not possible to exclude with absolute certainty that some NIU cases testing positive for HLA-B51 will not be reclassified as BD patients in the future. However, patients with any sign that could be attributable to BD were excluded from the NIU subgroup. In addition, given the natural inclination of BD to abate over time, the mean long-standing disease of NIU patients included in our study minimizes this risk of evolution.

Conclusions

To summarize, patients affected by NIU and testing positive for HLA-B51, irrespective of the associated systemic diagnosis, display a severe disease course that might potentially lead to a worse prognosis. The rate of long-term structural complications as well as visual acuity are similar between NIU unrelated to BD positive for HLA-B51 and BD-related uveitis. Patients testing positive for HLA-B51 are more likely to experience episodes of retinal vasculitis during the disease course. Therefore, individuals with NIU might be considered as possible candidates to undergo HLA-B typing, even if typical BD features are absent. They should be closely monitored with the aim to avoid the accumulation of irreversible ocular damage. Nevertheless, the prognostic role of HLA-B51 on such disease needs to be further explored with a more in-depth basic and clinical studies.

Author contribution statement

JS, LC and CF have designed the study and wrote the first draft. All authors have been involved in patients enrollment and revision of the manuscript. All authors have given final approval of the manuscript.

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