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COMPLICATION AND PROGNOSIS OF JUVENILE IDIOPATHIC ARTHRITIS ASSOCIATED UVEITIS IN THE ERA OF MODERN IMMUNOMODULATORY TREATMENT

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SUMMARY

JIA is the most common rheumatic disease of childhood and JIA-U is its most frequent and most devastating extraarticular manifestation. This form of uveitis is usually asymptomatic, chronic anterior uveitis, often accompained with complications. JIA-U is the main cause of vision loss and even blidness in childhood. Thus, screening for JIA-U in all JIA patients and early treatment is of prime importance. Over the last 15-20 years, ever since IMT has been used, studies generally show trends toward decrease of JIA-U onset, complications frequency, improvement of prognosis and remission achievement. Despite evident improvements, over 20% JIA-U patients still develop complications in long-term follow-up. Moreover, about 50% JIA-U patients continue to have active uveitis in adulthood. Therefore, JIA-U is still associated with high risk of late sequelae and visual acuity loss, functionally and structurally eye damage and quality of life impairment.

Key words: *juvenile idiopathic arthritis (JIA) - juvenile idiopathic arthritis-associated uveitis (JIA-U) - complication - prognosis - visual acuity - remission*

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogenous group of chronic inflammatory diseases, characterised primarily by arthritis of unknown etiology, which persists for a minimum of 6 weeks in a child younger than 16 years of age (Petty et al. 2004). JIA is the most common rheumatic disease of childhood (Ravelli et al. 2018). Epidemiologic studies of JIA prevalence report significantly variable results, from 7-150/100 000, and some authors estimate it to 400/100 000 children. Overall world incidence is 8.2 (7.5-9.0)/100 000 children younger than 16 years (Foeldvari et al. 2017, Prakken et al. 2011, Thierry et al. 2014).

Juvenile idiopathic arthritis-associated uveitis (JIA-U) is the most common extraarticular manifestation of JIA (Prakken et al. 2011, Carvounis et al. 2006, Heiligenhaus et al. 2007). JIA-U prevalence among JIA patients is from 11.6% up to 30% (Clarke et al. 2016, Yu et al. 2013, Sen et al. 2015, Tappeiner et al. 2016).

JIA-U is most frequently presented as asymptomatic anterior uveitis (iridocyclitis). JIA-U is characterised by chronic refractive course, accompanied by often vision-threatening complications (Sen 2015). Absence of classic symptoms triade (pain, conjunctival hyperemia, photophobia) hinders timely diagnose setting and therefore increases risk of complication development. This makes JIA-U an important clinical issue (Clarke et al. 2016). Asymptomatic uveitis is the most common JIA-U presentation and occurs typically in oligoarthritis JIA form. Symptomatic presentation occurs in only about 10% cases, typically within psoriatic arthritis and entezitis related athritis form (Linssen 1991).

Irreversible eye damage and vision loss prevention have developed trends toward more aggressive JIA-U treatment (Amin et al. 2015, Gregory et al. 2013). Direct correlation between number of anterior chamber (AC) inflammatory cells and severitiy of vision loss, make complete suppresion of intraocular inflammation (zero cells in AC) main JIA-U treatment target (Constantin et al. 2018, Ravelli et al. 2018, Gregory et al. 2013). Fundament of JIA and JIA-U treatment and first line therapy are local and/or systemic corticosteroids. Inflammation is usually chronic and demands long-term treatment. Regarding well-know corticosteroid side-effects, it is recommended to introduce immunomodulatory therapy (IMT), as corticosteroid-sparing agents. They include synthetic disease-modifying antirheumatic drugs (sDMARD) and biologic DMARD (bDMARD). In the transition to IMT, stepladder aproach is applied- sDMARD (most frequetly methotrexate (MTX)) as second line, and bDMARD (most frequently anti-TNF alfa) as third line treatment, for MTX-resistant or intolerant cases. Vigorous controls and early recognition of inadequate treatment response (within 3 months) is essential for therapy approach change. Timely switch to another treatment step leads toward better inflammation control and irreversible articular and extraarticular damage prevention (Bou et al. 2015, Foster et al. 2016, Consolaro et al. 2014, Tambić et al. 2013, Constantin et al. 2018).

JIA is one of the leading causes of acquired invalidity and life quality reduction in childhood. JIA-U is the main cause of vision loss and even blidness in childhood (Prakken et al. 2011). Recent investigations indicate that IMT has positive influence on complication rate reduction and visual prognosis improvement in patients with JIA-U. We searched available peer-reviewed publications regarding JIA-U complication and prognosis through base Web of Science (WOS), section Current Contents Connect-CCC and pubmed/MEDLINE, from year 1951. until June 2018.

INFLUENCE OF IMMUNOMODULATORY THERAPY ON JIA-U ONSET

Reduction of JIA-U frequency over time

JIA treatment strategies have significantly changed with the use of MTX in 1990s and bDMARD in 2000s and introduction of obligatory ophthalmologic screening on uveitis for all JIA patients in 1990s. (Giannini et al. 1992, Lerman et al. 2015, Cassidy et al. 2006, Heiligenhaus et al. 2007) Moreover, in the following period, increased sDMARD and bDMARD use was observed- from year 2002 to 2013, sDMARDs 39.8 to 47.2 % and bDMARDs from 3.3 to 21.8 % (Tappeiner et al. 2015). In this period, pharmacoepidemiological studies have started to register positive effects of IMT for JIA and JIA-U treatment. IMT use reduced risk for JIA-U onset and frequency of JIA-U in JIA patients (Foeldvari et al. 2005, Giannini et al. 1992, Tappeiner et al. 2016, Kostik et al. 2016, Papadopoulou et al. 2013). For example, in Switzerland, frequency of JIA-U among JIA patients was reduced from 16% in 1972., to 13% in 2005 (Bolt et al. 2008). Since than, there is a slower decline, according to extensive prospective data from German nacional JIA registry on over 18500 JIA patiets from 13% in 2002, to 11.6% in year 2013 (Tappeiner et al. 2015).

Early introduction of MTX and/or TNF inhibitors in JIA treatment, additionally reduces the risk of JIA-U development. Compared to patients with no DMARD treatment in the year before uveitis onset, the risk of uveitis was significantly decreased by MTX (hazard ratio [HR] 0.63, p=0.022), TNF inhibitors (HR 0.56, p=0.001) and by a combination of both (HR 0.10, p=0.001) (Tappeiner et al. 2016). Introduction of MTX within first year of JIA diagnosis reduced risk for JIA-U onset from 8.5% to 4.8% (HR 0.29, p<0.001) (Clarke et al. 2016, Tappeiner et al. 2015, Tappeiner et al. 2016).

There are still no clear recommendations about the need of profilactic MTX introduction for JIA patients as a prevention of JIA-U in patients with high risk for uveitis (ANA positive, oligoarthritis, younger age at JIA onset), despite satisfying arthritis control with first line treatment.

INFLUENCE OF IMT ON JIA-U COURSE AND PROGNOSIS

Visual impairment in JIA-U patients is consequence of the disease itself, but also due to the corticosteroid side-effects, like cataract and glaucoma (Clarke et al. 2016). IMT as corticosteroid-sparing agents, with its intense antiinflammatory acitvity, is able to improve JIA-U course and prognosis. IMT enables decrease in AC cells count, corticosteroid use, relapse number, complications frequency and visual loss during follow-up and finally, increases remission achievement frequency (Foeldvari et al. 2015, Paroli et al. 2015, Saurenmann et al. 2007, Heiligenhaus et al. 2018, Tappeiner et al. 2016).

Several factors associated with more severe course of uveitis and development of complications are: male gender, young age at onset of uveitis, longer disease duration, short interval between arthritis and uveitis, presence of synechiae and other complications at the time of first uveitis diagnosis and ANA positivitiy in oligoarticular JIA. (Gregory et al. 2013, Saboo et al. 2013, Sauernmann et al. 2007).

Future controlled trials and validated biomarkers research are nedded to set clear indications for earlier introduction of IMT for patients at high risk for severe uveitis course. (Heiligenhaus et al. 2015)

Influence on JIA-U complications frequency

Due to the asymptomatic course, 85% JIA-U cases remain unrecognised until the ophthalmologic screening examination is performed (Kotaniemi et al. 2005), when 20-45% patients already have ophthalmologic complications. Number of complications increase with time of follow-up. (Heiligenhaus et al. 2007, Heiligenhaus et al. 2015, Kanski 1977).

Risk for complications that reduce visual acuity is lower in JIA patients with symptomatic uveitis presentation (10% cases), because they visit ophthalmologiost earllier in the disease course, treatment starts timely and therefore have better prognosis (Linssen et al. 1991).

The most frequent complications are posterior synechiae, cataract and band keratopathy (Table 1). Complication with most influence on visual acuity loss is cataract, in 9-80%. It develops due to the chronic inflammation, but also intensive and long-term local and/or systemic corticosteroid use (Carvounis et al. 2006, Heiligenhaus et al. 2015).

One study showed that increased risk of cataract development in JIA-U patients does not depend on the uveitis severity or posterior synechia presence, but increases with local corticosteroid daily doses. Local corticosteroid eyedrops application ≤3 times daily during long-term follow-up (median 4 years, range 0.5-15 years), increases the risk for cataract development. None of the patients, which applied ≤2 doses daily did not develop cataract (Thorne et al. 2010).

Table 1. JIA-U complications (Heiligenhaus et al. 2013, Foeldvari et al. 2017, Tappeiner et al. 2015)

Complication	Frequency (%)
Posterior synechiae	8-75
Cataract	19-81
Band keratopathy	12-70
Vitreous opacities	7-10
Papilla edema	6-7
Secondary glaucoma	8-42
Macula edema	4-41
Bulbus hypotonia and phthysis	5-19
Rubeosis iridis	1-2

Studies report variable complication frequencies, probably due to the different patient selection criteria and follow-up time range (Foeldvari et al. 2017, Heiligenhaus et al. 2013, 2015, Tappeiner et al. 2015).

During follow-up time, in patients with active disease, frequency of complications increases significantly. Cataract was present in 42% at 7 years and in 51% at 24 years follow-up. Uveitic glaucoma was present in 5% at 7 years and in 22% at 24 years follow-up (Skarin et al. 2009).

However, better screening strategies and new treatment options lead to clear trends toward complication frequency decrease with time: 2-3 decades ago JIA-U complications frequency was 60-90% after 6-10 years of disease duration (Heiligenhaus et al. 2015, Wolf et al. 1987, Chalom et al. 1997) A prospective, cross-sectional study from Germany including 18,555 JIA patients between 2002 and 2013 found additional decrease in uveitis complications from 33.6 to 23.9 % (OR 0.94, $p<0.001$) (Tappeiner et al. 2015). Thus, despite reduction over time, over 20% JIA-U patients still develop complications in long-term follow-up. Therefore, JIA-U is still associated with high risk of late sequelae and visual acuity loss (Thorne et al. 2007, DeBoer et al. 2003).

Influence on visual acuity loss

Improvements in JIA and JIA-U management result in improvement of visual acuity (VA) prognosis in the last three decades (Zak et al. 2003, Haasnoot et al. 2016, Schenck et al. 2014, Lerman et al. 2015) (Table 2).

Significant differences in VA prognosis depend on AC inflammatory cells count- complete absence of cells does not increase risk, while even a small number of AC cells increases risk for visual acuity deterioration. Presence of cells in AC during first diagnosis setting, or during follow-up, results in 2x higher risk for VA ≤20/50 and 3x for VA ≤20/200 (legally blindness). (Thorne et al. 2007, Gregory et al. 2013).

VA loss may be present at first assessment with VA of ≤20/50 in 40.3% and ≤20/200 in 24.2% at presentation (Gregory et al. 2013).

In meta-analysis looking at outcomes in JIA-U showed that cumulative VA loss (VA<20/40 both eyes together) is 9.2% in JIA-U patients (Carvounis 2006). Since cumulative worldwide JIA-U incidence is 8.3%, a child with JIA has risk for bilaterally severly damaged VA of 1% (Heiligenhaus et al. 2013), which is a lot favorable outcome than in the beginning of 1970s (before IMT era), when 36% JIA-U patients were legally blind (Thorne et al. 2010, Hassnoot et al. 2016)

INFLUENCE OF IMT ON REMISSION ACQUIREMENT

In the past, it was considered that joint and eye inflammation would „burn out“ during puberty. Recent studies on adult JIA patients showed that even with cDMARD, about 60% patients after 5 years still have active uveitis. In one Dutch study, in the age of 18, only 8% patients were in remission, 73% was taking some of the IMT, and 4% was legally blind on both eyes. (Haasnoot 2016)

However, a prospective, cross-sectional study from Germany including 18,555 JIA patients between 2002 and 2013 found a significant increase in achieving uveitis inactivity during follow-up- 30.6% in 2002 and 65.3% in 2013 (OR=1.15, $p<0.001$) (Tappeiner et al. 2016).

In the adulthood, activity of JIA and JIA-U still persist in a large percent of patients- remission is accomplished in 40-60% for arthritis (Ravelli 2004) and only 50% for uveitis, even with modern DMARD treatment, so a great number of patients has to continue treatment in the adult age. Outcomes differ among studies due to the variable follow-up time and patient selection (Hassnoot et al. 2016, Kotaniemi et al. 2005, Vidqvist et al. 2013).

Predictors for JIA-U extension into adult age are: late onset uveitis and arthritis, HLA-B27 positivity, presence of complications on the first ophthalmologic examination (Gregory et al. 2013, Foeldvari et al. 2017).

Table 2. Frequency of visual acuity impairment and legally blindness in JIA-U patients over time

Time range	Frequency visual acuity loss in JIA-U patients	Legally blind (<20/200) JIA-U patients	Reference
Before 1990	58%	1967. 36%	Thorne et al. 2010, Hassnoot et al. 2016
Early 1990s	18-30%	1992. 17.6%	Carvounis et al. 2006, Hassnoot et al. 2016
2000s	<0.5 Snellen - 3.4%	1-5.6%	Bolt et al. 2008, Carvounis et al. 2006, Sabri et al. 2008, Zak et al. 2003

JIA-U: juvenile idiopathic arthritis-associated uveitis

INFLUENCE OF NEW JIA AND JIA-U TREATMENT STRATEGIES ON TREATMENT COST

JIA imposes the social burden because of the treatment costs. 30 years ago, annual cost assessment for a child with JIA was 7905 USD. Since bDMARD implementation, costs have multiplied (Allaire et al. 1992). Recently, a few direct annual costs are estimated to 1900-2700 Eur (Bernatzky et al. 2007, Haapasaari et al. 2004). Although the number of children with JIA does not have a large share in the total population, these are high-risk patients, with high treatment cost, whose impairment and often treatment, continues to adulthood (Oen et al. 2002). Therefore, treatment cost and avoidance of complications in childhood, needs to be perceived in the light of prevention of longlife pain, dissabilities and impaired quality of life. In adulthood, indirect costs take over the highest cost- limitations in work and sick leave (Minden et al. 2004).

Trends toward decrease the rate of complications and improvement of prognosis, could possibly reverse cost-benefit analysis in favour of use IMT, despite its high price.

CONCLUSION

JIA-associated uveitis is the commonest extra-articular manifestation of JIA with significant numbers of children still developing sight-threatening complications. Regular screening with slit lamp examination is essential for early diagnosis, and early IMT introduction for JIA, provides avoidance of steroid-related side effects. There are suggestions that both JIA-U prevalence and frequency of complications is decreasing over time, since introduction of DMARD in JIA treatment- visual acuity loss rate was up to 30 % before 1900s, and was reduced to less than 5% lately (Carvounis et al. 2006).

However, VA loss cannot be the only weight of the disease consequences. JIA-U complexity and influence on functionally and structural eye damages (visual field, eye phthysis,...), need for eye surgeries, frequent IMT aplications are factors that impaire quality of life and make multivariable frame for assesment of burden of the disease (Heiligenhaus et al. 2013).

Considering wide range of incidence and prevalence reports, and wide range of reported complications (Table 1), it is hard to assess true changes of complications over tie, but available studies generally do show trends toward decrease of complications frequency and improvement of prognosis and remission achievement in last 15-20 years.

Experience about JIA-U management is collected slowly, due to the low prevalence of these patients in general, moreover, not all of them require IMT. (Heiligenhaus et al. 2012, Ramanan et al. 2017, Siddique et al. 2011). Multicentric controlled studies are needed in order to assess true IMT role in longterm JIA-U complications and prognosis.

The current issue is also whether prompt introduction of DMARDs is justifiably in JIA patients at high risk for uveitis, regardless of arthritis condition, as prevention of uveitis itself. (Heiligenhaus 2018) Future studies, biomarker research and clinical practice should focus on recognition of patients at high risk for severe uveitis course and evaluation of benefit of early IMT introduction for those patients.

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Contribution of individual authors:

Marija Barišić Kutija & Nenad Vukojević had substantial contribution to the conception and design of the study.

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References

1. *Allaire SH, DeNardo BS, Szer IS, Meenan RF, Schaller JG: The economic impacts of juvenile rheumatoid arthritis. J Rheumatol 1992; 19:952-55*
2. *Amin RM, Miserocchi E, Thorne J, Hornbeak D, Jabs DA, Zierhut M: Treatment Options for Juvenile Idiopathic Arthritis (JIA) Associated Uveitis. Ocular Immunology and Inflammation 2016; 24:81-90*
3. *Bernatzky S, Duffy C, Malleson P, Feldman DE, St Pierre Y, Clarke AE: Economic impact of juvenile idiopathic arthritis. Arthritis Rheum 2007; 57:44–48*
4. *Bolt JB, Cannizzaro E, Seger R, Saurenmann RK: Risk factors and long-term outcome of juvenile idiopathic arthritis-associated uveitis in Switzerland. J Rheumatol 2008; 35:703–706*
5. *Bou R, Adán A, Borrás F, Bravo B, Calvo I, De Inocencio J et al.: Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int 2015; 35:777-85*
6. *Carvounis PE, Herman DC, Cha S, Burke JP: Incidence and outcomes of uveitis in juvenile rheumatoid arthritis, a synthesis of the literature. Graefe´s Arch Clin Exp Ophthalmol 2006; 244:281–90*
7. *Cassidy J, Kivlin J, Lindsley C, Nocton J: Ophthalmologic examinations in children with juvenile rheumatoid arthritis. Pediatrics 2006;117:1843–5*
8. *Chalom EC, Goldsmith DP, Koehler MA: Prevalence and outcome of uveitis in a regional cohort of patients with juvenile rheumatoid arthritis. J Rheumatol 1997; 24:2031–4*

9. *Clarke SL, Sen ES, Ramanan: Juvenile idiopathic arthritis-associated uveitis. Pediatr Rheumatol 2016; 14:27*
10. *Consolaro A, Bracciolini G, Ruperto N, Pistorio A,Magni-Manzoni S,Malattia C et al.: Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. Arthritis Rheum 2012; 64:2366–74*
11. *Consolaro A, Ruperto N, Bracciolini G, Frisina A, Gallo MC, Pistorio A et al.: Defining criteria for high disease activity in juvenile idiopathic arthritis based on the juvenile arthritis disease activity score. Ann Rheum Dis 2014; 73:1380–3*
12. *Constantin T, Foeldvari I, Anton J, de Boer J, Czitrom-Guillaume S, Edelsten C et al.: Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. Ann Rheum Dis 2018; 77:1107-1117*
13. *De Boer J, Wulffraat N, Rothova A: Visual loss in uveitis of childhood. Br J Ophthalmol 2003; 87:879–84*
14. *Foeldvari I, Wierk A: Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol 2005; 32:362-5*
15. *Foeldvari I, Becker I, Horneff G: Uveitis Events During Adalimumab, Etanercept, and Methotrexate Therapy in Juvenile Idiopathic Arthritis: Data From the Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken) 2015; 67:1529-35*
16. *Foeldvari I, Walscheid K, Heiligenhaus A: Uveitis in juvenile idiopathic arthritis. Z Rheumatol 2017; 76:664-672*
17. *Foster CS, Kothari S, Anesi SD, Vitale AT, Chu D, Metzinger JL et al.: The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. Surv Ophthalmol 2016; 61:1-17*
18. *Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I et al.: Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med 1992; 326:1043-9*
19. *Gregory AC, Kempen JH, Daniel E, Kaçmaz RO, Foster CS, Jabs DA, et al.: Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study Research Group. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the Systemic Immunosuppressive Therapy for Eye Diseases Study. Ophthalmology 2013; 120:186-9*
20. *Haapasaari J, Kautiainen HJ, Isoma ¨ki HA, Hakala M: Etanercept does not essentially increase the total costs of the treatment of refractory juvenile idiopathic arthritis. J Rheumatol 2004; 31:2286–2289*
21. *Haasnoot AJ, Vernie LA, Rothova A, V D Doe P, Los LI, Schalij-Delfos NE et al.: Impact of juvenile idiopathic arthritis associated uveitis in early adulthood. PLOSONE 2016; 11:e0164312*
22. *Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K: Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology (Oxford) 2007; 46:1015–9*
23. *Heiligenhaus A, Michels H, Schumacher C et al.: Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Rheumatol Int 2012; 32:1121-33*
24. *Heiligenhaus A, Minden K ,Foll D, Pleyer U: Uveitis in juvenile idiopathic arthritis. Dtsch Arztebl Int 2015; 112:92–100*
25. *Heiligenhaus A, Minden K, Tappeiner C, Baus H, Bertram B, Deuter C, Foeldvari I, Föll D, Frosch M, Ganser G, Gaubitz M, Günther A, Heinz C, Horneff G, Huemer C, Kopp I, Lommatzsch C, Lutz T, Michels H, Neß T, Neudorf U, Pleyer U, Schneider M, Schulze-Koops H, Thurau S, Zierhut M, Lehmann HW: Interdisziplinäre Leitlinie zur Diagnostik und antientzündlichen Therapie der Uveitis bei juveniler idiopathischer Arthritis 2018 Register Nr. 045/012 Klasse: S2k*
26. *Kanski JJ: Anterior uveitis in juvenile rheumatoid arthritis. Arch Ophthalmol 1977; 95:1794–1797*
27. *Kostik MM, Gaidar EV, Hynnes AY, Dubko MF, Masalova VV, Snegireva LS et al.: Methotrexate treatment may prevent uveitis onset in patients with juvenile idiopathic arthritis: experiences and subgroup analysis in a cohort with frequent methotrexate use. Clin Exp Rheumatol 2016; 34:714-8*
28. *Kotaniemi K, Arkela-KautiainenM, Haapasaari J et al.: Uveitis in young adults with juvenile idiopathic arthritis: a clinical evaluation of 123 patients.AnnRheumDis 2005; 64:871–874*
29. *Lerman MA, Rabinovich CE: The Future Is Now: Biologics for Non-Infectious Pediatric Anterior Uveitis. Paediatr Drugs 2015; 17:283-301*
30. *Linssen A, Rothova A, Valkenburg HA, et al.: The lifetime cumulative incidence of acute anterior uveitis in a normal population and its relation to ankylosing spondylitis and histocompatibilty antigen HLA-B27. Invest Ophthalmol Vis Sci 1991; 32:2568–78*
31. *Minden K, Niewerth M, Listing J, et al.: Burden and cost of illness in patients with juvenile idiopathic arthritis. Ann Rheum Dis 2004; 63:836–842*
32. *Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M: Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. J Rheumatol 2002; 29:1989-99*
33. *Papadopoulou C, Kostik M, Böhm M, et al.: Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. J Pediatr 2013; 163:879–84*
34. *Paroli Mp, Abbouda A, restivo L, et al.: Juvenile idiopathic arthritis-associated uveitis at an Italian tertiary referral center: clinical features and complications. Ocul Immunol Inflamm 2015; 23:74–81*
35. *Petty RE, Southwood TR, Manners P: International league of associations for rheumatology. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004; 31:390–392*
36. *Prakken B, Albani S, Martini A: Juvenile idiopathic arthritis. Lancet 2011; 377:2138–49*
37. *Ramanan AV, Dick AD, et al.: Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. N Engl J Med 2017; 376:1637-46*
38. *Ravelli A: Toward an understanding of the long-term outcome of juvenile idiopathic arthritis. Clin Exp Rheumatol 2004; 22:271–5*

39. Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, Wulffraat NM: Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis 2018; 77:819-828
40. Saboo US, Metzinger JL, radwan A, et al.: risk factors associated with the relapse of uveitis in patients with juvenile idiopathic arthritis: a preliminary report. J Aapos 2013; 17:460–4
41. Sabri K, Saurenmann RK, Silverman ED & Levin AV: Course, complications, and outcome of juvenile arthritis-related uveitis. J AAPOS 2008; 12:539–545
42. Saurenmann RK, Levin AV, Feldman BM, et al.: Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. Arthritis Rheum 2007; 56:647–57
43. Sen ES, Dick AD, Ramanan AV: Uveitis associated with juvenile idiopathic arthritis. Nat Rev Rheumatol 2015; 11:338-48
44. Schenck S, Klotsche J, Niewerth M, et al.: Inzidenzanalyse der JIA – assoziierten Uveitis im zeitlichen Verlauf (2000–2012). Monatsschr Kinderheilkd 2014; 162:252
45. Siddique SS, Shah R, Suelves AM, Foster CS: Road to remission: a comprehensive review of therapy in uveitis. Expert Opin Investig Drugs 2011; 20:1497-515
46. Skarin A, Elborgh R, Edlund E, Bengtsson-Stigmar E: Long-term follow-up of patients with uveitis associated with juvenile idiopathic arthritis: a cohort study. Ocul Immunol Inflamm 2009; 17:104–8
47. Tambić Bukovac L, Vidović M, Lamot L, Perica M, Harjaček M: Guidelines on biologic drugs for the treatment of children with juvenile idiopathic arthritis (JIA). Reumatizam 2013; 60
48. Tappeiner C, Klotsche J, Schenck S, Niewerth M, Minden K, Heiligenhaus A: Temporal change in prevalence and complications of uveitis associated with juvenile idiopathic arthritis: data from a cross-sectional analysis of a prospective nationwide study. Clin Exp Rheumatol 2015; 33:936-44
49. Tappeiner C, Schenck S, Niewerth M, Heiligenhaus A, Minden K, Klotsche J: Impact of Antiinflammatory Treatment on the Onset of Uveitis in Juvenile Idiopathic Arthritis: Longitudinal Analysis From a Nationwide Pediatric Rheumatology Database. Arthritis Care Res (Hoboken) 2016; 68:46-54
50. Thorne JE, Woreta F, Kedhar SR, et al.: Juvenile idiopathic arthritis-assoacited uveitis: incidence of ocular complications and visual acuity loss. Am J Ophthalmol 2007: 143:840–6
51. Thorne JE, Woreta FA, Dunn JP, Jabs DA: Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology 2010; 117:1436–1441
52. Thierry S, Fautrel B, Lemelle I, Guillemin F: Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine 2014; 81:112-7
53. Vidqvist KL, Malin M, Varjolahti-Lehtinen T, Korpela MM: Disease activity of idiopathic juvenile arthritis continues through adolescence despite the use of biologic therapies. Rheumatology 2013; 52:1999–2003
54. Wolf MD, Lichter PR, Ragsdale CG: Prognostic factors in the uveitis of juvenile rheumatoid arthritis. Ophthalmology 1987; 94:1242–8
55. Yu HH, Chen pC, Wang LC, Lee JH, Lin YT, Yang YH et al: Juvenile idiopathic arthritis-associated uveitis: a nationwide population-based study in Taiwan. PLoS One 2013; 8:e70625
56. Zak M, Fledelius H, Pedersen FK: Ocular complications and visual outcome in juvenile chronic arthritis: a 25-year follow-up study. Acta Ophthalmol Scand 2003; 81:211-5

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