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Non-anti-TNF biologic modifier drugs in non-infectious refractory chronic uveitis: The current evidence from a systematic review

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ABSTRACT

Objective: To examine, separately, in children and adults with autoimmune chronic uveitis (ACU), the evidence regarding the effectiveness and the safety of switching to a non-anti-TNF biologic modifier immunosuppressant treatment (NTT) currently available in clinical practice.
Methods: A systematic search between January 2000 and April 2014 was conducted using EMBASE, Ovid MEDLINE, Evidence Based Medicine Reviews—ACP Journal Club, Cochrane libraries, and EBM Reviews. Studies investigating the efficacy of NTT as a biologic modifier immunosuppressant medication for ACU, refractory to topical and/or systemic steroid therapy, were eligible for inclusion. The primary outcome measure was the improvement of intraocular inflammation, as defined by the SUN working group criteria. We determined a combined estimate of the proportion of subjects responding to NTT.
Results: We initially identified 526 articles, of which 89 were potentially eligible. From the selection process, a total of 10 retrospective chart reviews and a randomized single-blind controlled study, providing a total of 12 children and 34 adults, were deemed eligible: 3 articles looked at rituximab, 3 at abatacept, 3 at tocilizumab, and the remaining 1 at alemtuzumab and the other at anakinra. Before the NTT treatment, all the eligible subjects received several combinations of one or more DMARDs and at least one anti-TNF strategy. With the exclusion of 7 adults enrolled in the RCT, 8 of 12 children and 18 of 27 adults responded to NTT treatment: 0.66 was the combined estimate of the proportion of subjects improving on NTT treatment in children (95% CI: 0.46 – 0.99) and in adults (95% CI: 0.49–0.84). Further statistical comparison between different NTT strategies was not possible due to the small sample size.
Conclusion: Although randomized controlled trials are needed, the available evidence suggests the clinical use of a NTT strategy in selected categories of ACU, refractory to previous course of immunosuppressive treatment, DMARDs, as well as anti-TNFα, in adults as well as children.

Introduction

Non-infectious chronic uveitis is a serious and disabling sight-threatening disease accounting for up to 10% of pathologies leading to blindness [1]. Currently, a step-by step escalating immunosuppressive therapy is generally used, in children as well as in adults, and anti-TNFα biologic therapies have markedly increased the treatment options for sight-threatening uveitis refractory to conventional immune-modulatory therapy (DMARD) in addition to topical and/or systemic corticosteroids [2,3]. However, a subset of patients fails to respond to TNFα blockers or is unable to tolerate these therapies and may therefore benefit from switching to another drug [4,5]. Overall, about 25% of children with autoimmune chronic uveitis (ACU) who received adalimumab and infliximab do not respond to these treatments [6]. In this clinical setting, the availability of several different molecules, mostly off-label, poses the clinical question whether it can be useful and safe to administer another class of biologic drugs, such as abatacept or rituximab, for patients with refractory autoimmune uveitis. To the best of our knowledge, to date, there has been no systematic evaluation on this topic. However, efficacy, availability of systemic treatments, as well as their potential side effects can be different between adults and children. The aim of our study was therefore to examine, separately, in children and adults with autoimmune chronic uveitis (ACU), the evidence regarding the effectiveness and the safety of switching to a non-anti-TNF biologic response modifier immunosuppressant treatment (NTT) currently available in clinical practice.

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Methods

A systematic review was conducted and is reported according to the PRISMA guidelines.

Eligibility criteria

For a study to be eligible, patients were required to (1) have vision-threatening non-infectious autoimmune uveitis; (2) have autoimmune uveitis refractory to topical and/or systemic steroid treatment, thus showing a chronic disease course with regard to immunosuppressive therapy according to the Standardization of Uveitis Nomenclature (SUN) criteria definition, that is, persistent uveitis characterized by relapse within 3 months after discontinuation of therapy; and (3) commence one of the currently available NTT treatments as a biologic modifier immunosuppressant medication for the treatment of chronic uveitis. Further, to be eligible, the included studies required (a) outcome measures that assessed the effectiveness of NTTs according to the SUN criteria for reporting clinical data or provided sufficient data from which we could extract this information [7,8]; (b) to include at least a 6 ($\pm$2)-month period of follow-up on treatment, and we included this time-related inclusion criterion in order to avoid a potential bias in judging the effect treatment due to the different follow-up period of each study; and (c) to be reported in English language.

Exclusion criteria were the following: (1) lack of applicability/adherence to the SUN working group criteria definition of improvement in uveitis activity, (2) individual case reports, and (3) articles from which we would not be able to extract data separately in adults and children. Patients have been considered as adults if the starting time of NTT administration was after 16 years of age.

Outcome measures

The main outcome measure used to assess the effect of NTTs on disease was the improvement of intraocular inflammation considered as Tyndall (anterior chamber cells), according to the definition of improvement of the SUN working group criteria [5]. Anterior chamber inflammation was considered "inactive" or controlled if the inflammatory activity was grade 0 cells. The SUN working group grading scheme for anterior chamber activity varies from 0 to 4+ and reflects the number of cells in a field that is the size of 1 $\times$ 1 mm slit beam. Regarding posterior inflammation, the National Eye Institute system for grading vitreous haze was adopted, and the designation "trace" was recorded as 0.5+. Uveitis was defined as improved, and NTT TNFα treatment as successful, when its activity decreased by 2 steps in the level of inflammation (anterior chamber cells and/or vitreous haze) or decreased to grade 0 [5] at least at 6-month follow-up ($\pm$2). For studies not adherent to the SUN criteria, we applied the SUN activity terminology with regard to reported activity grading, where possible, and only an activity grade of 0 was considered as improvement. If one eye improved, but the other eye worsened, the judgment was increased activity, and the effect of treatment was considered as failure.

As secondary outcomes, tapering and/or stopping systemic steroid administration, improvement in visual acuity after treatment, discontinuation of treatment, time to remission (the duration of treatment needed to achieve remission-inactive disease), time in remission on therapy (the duration of on-going/persistent remission, while treatment is continued) and time in remission off therapy (the period with on-going/persistent remission after discontinuing treatment and off therapy), and safety of administered drug were also considered, when reported. Regarding visual acuity outcome, "normal" acuity was defined as at least a best-corrected visual acuity (BCVA) of 20/25 (0.8 in a decimal scale = 0.10 in a logMAR format). "Improved" visual acuity was defined as a doubling of the visual angle (converted into a logMAR format) in at least one eye. Conversely, "worsened" visual acuity was defined as a halving of the visual angle at a logMAR format from baseline in at least one eye (corresponding to an increase or decrease of 3 lines on a decimal scale with a logarithmic chart) [6]. The proportion of patients improved or stable in normal values at complete or nearly complete follow-up was considered the outcome of interest in visual acuity, according to the SUN working group criteria [6]. If these data were not extractable from the article, the information was considered missing.

Information sources

Publications included in the present review were retrieved using a computerized search of the following databases: EMBASE, Ovid MEDLINE, Evidence Based Medicine Reviews—ACP Journal Club, EBM Reviews—Cochrane Central Register of Controlled Trials, EBM Reviews—Cochrane Database of Systematic Reviews, and EBM Reviews—Database of Abstracts of Reviews of effects. Publications between January 2000 and April 2014 were included in this review.

Search strategy

Databases were searched with the keywords "chronic uveitis" OR "chronic iridocyclitis" OR "recurrent uveitis" OR "refractory uveitis" OR "non-infectious uveitis" OR "autoimmune uveitis" OR "inflamma$ ocul$" OR "inflamma$ eye," and were crossed with "Abatacept" OR "Rituximab" OR "tocilizumab" OR "Anakinra" OR "canakinumab" OR "cytotoxic T-lymphocyte-associated antigen-4" OR "CTLA-4" OR "monoclonal IgG1 antibody against CD20" OR "CD-20" OR" IL-1 receptor antagonist" OR "antagonist" OR "IL-1β blocking antibody" OR" Anti-Il-6 receptor monoclonal antibody" OR "Anti-IL-6" OR "Anti-IL-1" OR" monoclonal antibodies" OR "biologics drugs." No limitation with regard to the type of the study was entered. This strategy excluded records related to infectious and/or suppurative uveitis.

Study selection

Two reviewers independently screened the retrieved titles and abstracts and excluded duplicates, those obviously irrelevant, and articles related to infectious and/or suppurative uveitis. If the information in the abstracts was insufficient to make a decision, full text was retrieved. Full text of the selected articles was examined to determine whether they satisfied the criteria, and this was confirmed by a second reviewer. The references of all eligible articles including reviews, expert-opinion articles, and systematic reviews were manually searched for potentially eligible publications. During consensus meetings, disagreements of selections were resolved. In addition, we contacted authors of studies to determine whether data on eligible sub-group were available.

Data extraction and items

Data were extracted by a single reviewer using a standard form and checked by a second reviewer. The data items extracted were study design, study start/end dates, length of follow-up, aim of the study, characteristics of participants (number of children, gender, age, and associated conditions), dose of NTT, previous DMARD and/or anti-TNFα treatment, and all outcome measures.