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INFLAMMATORY DISORDERS

Discontinuation of long-term adalimumab treatment in patients with juvenile idiopathic arthritis-associated uveitis

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Abstract
Purpose The purpose of this study was to evaluate the discontinuation of adalimumab (ADA) treatment in patients with juvenile idiopathic arthritis-associated uveitis (JIAU).
Methods Patients in whom ADA treatment was initiated for JIAU were included in this retrospective analysis. Reasons for discontinuing ADA treatment in patients with primary treatment response were analysed.
Results Within a group of 387 JIAU patients, 59 of 68 patients who were treated with ADA achieved a sufficient response to treatment within 6 months. Here, 39 patients (66.1 %) were still on therapy at their last follow-up visit (mean treatment duration of 38.3 months, range 12–91). In another 20 patients, ADA had been discontinued after 1 or 2 years or later, in 10 % ($n = 2$), 45 % ($n = 9$) and 45 % ($n = 9$) of patients, respectively (mean 30.6 months; range 10–65). Reasons for discontinuing ADA were reactivation of uveitis ($n = 8$, 3.93 per 100 patient-years) or arthritis ($n = 4$; 1.97 per 100 patient-years), or ≥2 years of complete disease inactivity ($n = 3$, 1.47 per 100 patient-years), adverse events ($n = 4$; 1.89 per 100 patient-years), or other ($n = 1$; 0.47 per 100 patient-years).
Conclusions The data show a good primary response to ADA in patients with refractory JIAU. Due to the increasing rate of adalimumab failure or adverse events during long-term treatment, further treatment options may be required.

Keywords Adalimumab · Biological disease-modifying anti-rheumatic drug · Juvenile idiopathic arthritis · Uveitis

Introduction

Juvenile idiopathic arthritis (JIA) represents a heterogeneous group of chronic arthritis diseases manifesting before the age of 16 years [1] that is frequently associated with chronic non-infectious uveitis [2–5]. Risk factors for developing uveitis are early onset of JIA, subtype of oligoarthritis, antinuclear antibody positivity, and others [6, 7]. JIA-associated uveitis (JIAU) may lead to ocular complications and, therefore, bears a significant risk for visual loss [8–13].

A stepladder approach has been suggested for treating JIAU patients [12, 14, 15], starting with topical corticosteroids, eventually adding systemic corticosteroids, and then giving conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), particularly methotrexate, as a next step. In treatment-refractory cases, tumour necrosis factor (TNF)-alpha inhibitors, which are biological DMARDs (bDMARDs), are used. Infliximab and adalimumab (ADA) demonstrated effectiveness in refractory JIAU, with ADA currently being the preferred drug [16, 17]. Vazquez-Cobian and colleagues showed a decrease in inflammation in 21 out of 26 eyes (80.8 %) of 14 children with uveitis ($n = 9$ for JIA-

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associated, and an additional $n = 5$ for idiopathic disease) by using ADA for an average of 18.1 months of treatment [18]. Biester et al. reported effectiveness of ADA in 16 of 18 patients with refractory JIAU. In four of the 18 patients, ADA had to be stopped before 6 months of treatment duration due to ineffectiveness or side effects of the drug [19].

The aim of the present study was to analyse the reasons for discontinuing ADA in JIAU patients who showed a primary treatment response to this drug.

Material and methods

A retrospective chart review was performed at the Department of Ophthalmology at St. Franziskus Hospital in Muenster, Germany. For this type of study, formal consent is not required. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

From all JIAU patients found in the database, patients were identified who had received ADA treatment at any time between March 2006 and July 2013. The diagnosis of JIA was based on criteria defined by the ILAR [1] and was confirmed at specialized paediatric rheumatology centres. The presence of antinuclear antibodies (ANA), HLA-B27 antigen and rheumatoid factor (RF) were documented.

In all of these patients, treatment with ADA (Humira®, AbbVie, Wiesbaden, Germany) was initiated if uveitis either with or without active arthritis was refractory to both topical and systemic corticosteroids and to at least one csDMARD, or if the patients did not tolerate such medication. All patients had previously received, at least once, a temporal course of high dosages of topical (e.g., prednisolone acetate 1 %, up to hourly) and systemic corticosteroids (prednisone equivalent ≥1 mg/kg body weight) with subsequent tapering. Uveitis was considered refractory if activity persisted despite at least 6 months of treatment.

Before starting ADA, we had ensured that health insurance would cover the cost of therapy, obtained written informed consent because of the off-label situation and excluded tuberculosis, other chronic infections (e.g., hepatitis B or C) and any findings typical for multiple sclerosis. Patients were followed up routinely by an ophthalmologist and paediatric rheumatologist.

ADA dosage was adjusted to 24 mg/m^2 body surface, up to a maximum of 40 mg subcutaneously every other week. Concomitant topical corticosteroids were attempted to taper to a maintenance dosage of ≤2 applications daily.

According to the SUN classification [20], all JIA patients suffered from chronic non-granulomatous anterior uveitis. An anterior chamber cell grade of ≥0.5+ was defined as active uveitis [20]. At least every 3 months, the clinical data on uveitis activity and structural complications were recorded [21].

The analysed parameters included age, gender, age at onset of uveitis, anatomical location of uveitis, uni- or binocular involvement, baseline and current best-corrected visual acuity (BCVA; measured and transformed into logMAR for statistical analysis), anti-inflammatory therapy for uveitis, age at ADA institution, and any uveitis-related eye complications.

Insufficient response to ADA treatment within the first 6 months was defined as primary treatment failure, and these patients were excluded for the further analysis. Only patients in whom ADA treatment achieved uveitis inactivity within 6 months (first response) were selected for our further studies [14, 20]. The primary outcome measure was the discontinuation of ADA after ≥6 months of treatment, defined as secondary treatment failure. Our composite outcome measure for treatment response included uveitis inactivity, no uveitis flares, visual acuity improvement, sparing of corticosteroids, disappearance of macular oedema and no worsening. Treatment failure with respect to uveitis was defined as an ≥2 step increase in the level of anterior chamber cell grade, visual loss or the development of complications related to active uveitis, such as new synechiae formation, dense vitreous cell infiltration or macular oedema [14, 20]. Any worsening of arthritis was documented [21]. Additionally, adverse events and any other reasons for withdrawing ADA were analysed.

All data analyses and descriptive statistics were conducted using MedCalc statistical software version 11.6 (MedCalc Software bvba, Ostend, Belgium).

Results

Patient group

Of a total of 387 JIAU patients from our database, 68 patients (18 %) were treated with ADA (Fig. 1). The mean duration of ADA treatment for these 68 patients was 34.5 months (SD ± 28.4, median 30.6, range 3–91 months). The patients (female 79.4 %, ANA positivity 85.3 %) were suffering from oligoarthritis (persistent and extended, $n = 60/88.2$ %) or polyarthritis ($n = 8/11.8$ %) with associated anterior uveitis (Table 1). At the start of ADA, the mean age was 11.6 years, the mean uveitis duration was already 6.3 years, and eye complications were present in 72.1 % of patients. All patients were on topical and systemic corticosteroids and at least one csDMARD, mainly methotrexate (76.5 %), azathioprine (17.6 %) or cyclosporine A (14.7 %) at baseline directly before the institution of adalimumab, and they were generally continued when adalimumab was instituted. Eight patients (11.8 %) had already been treated with another TNF inhibitor (Table 2).

ADA was effective with a sufficient primary response in 59 patients (86.8 %) within 6 months of treatment (Fig. 1).

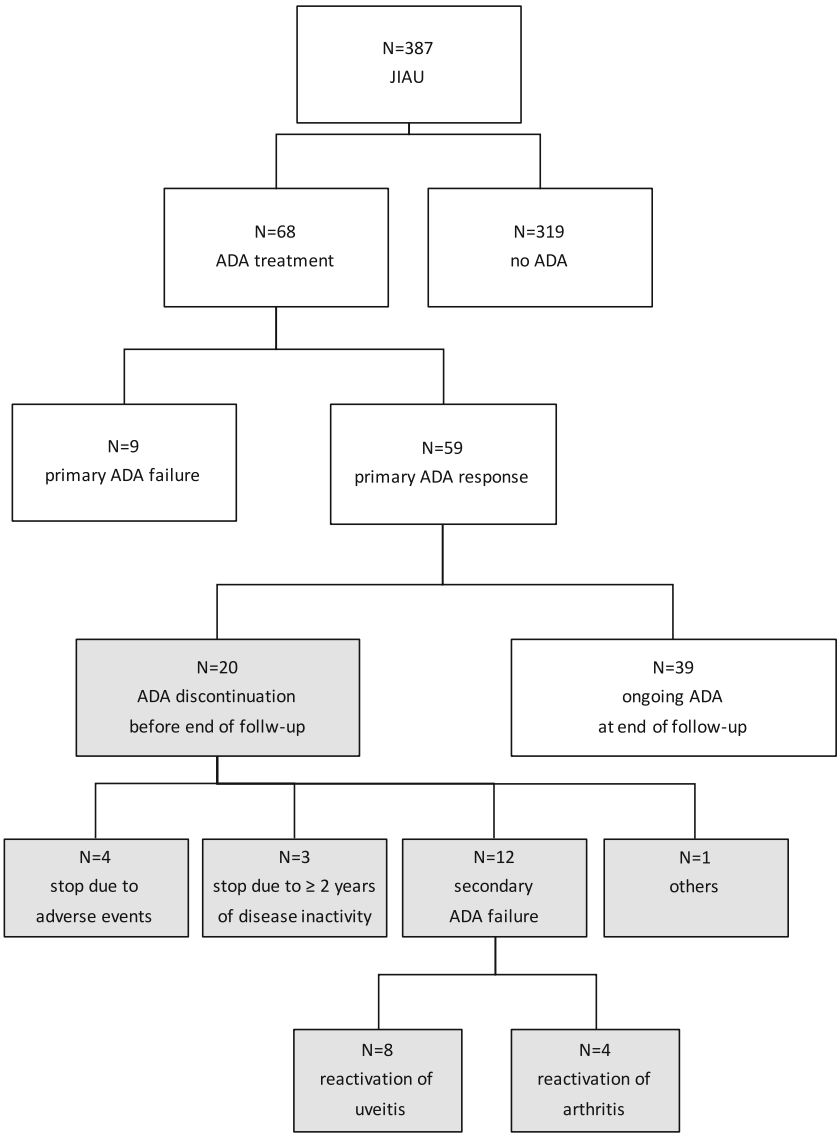

Fig. 1 Flow-chart of adalimumab (ADA) treatment in patients with juvenile idiopathic arthritis-associated uveitis (JIAU). Number of patients with primary drug response or failure, and with ongoing or discontinued treatment at the end of follow-up are shown

Uveitis inactivity was achieved with ADA after a mean of 3.4 months (SD ± 1.8) and arthritis inactivity after a mean of 3.6 months (SD ± 1.6). With ADA, both topical (97.1 %) and systemic corticosteroids (86.5 %) and csDMARDs (16.4 %) could be spared.

Discontinuation of adalimumab treatment

At the time of data analysis, 39 of the 59 patients (66.1 %) were still on ADA therapy, with a mean treatment duration of 38.3 months (SD 22.5, median 34.5, range 12–91). In all of them, ADA was still effective for both uveitis and arthritis. In another 20 patients, ADA had been discontinued after a mean of 30.6 months (SD 19.3, median 21.6, range 10–65) of treatment (Fig. 2). This corresponds to stopping ADA treatment after 1, 2 or more years in two patients (10 %), nine patients (45 %), and another nine patients (45 %), respectively.

ADA was discontinued in 12 of these 20 patients (60 %) due to a loss of treatment response (secondary failure). In eight of them, uveitis recurred under treatment and was active at least at two consecutive 3-month visits, despite increasing the topical corticosteroids and maintaining ≥4 times daily dosages. ADA was discontinued in these patients after 10–65 months of treatment (loss of ADA treatment response for uveitis: 3.93 per 100 patient-years). Notably, none of the six patients who started ADA already during ≤12 months after uveitis manifestation showed loss of treatment response to the drug and subsequent discontinuation of treatment during the observation period.

In another four of the patients, ADA was discontinued at 12–47 months of therapy because arthritis had reactivated (loss of ADA treatment response for arthritis 1.97 per 100 patient-years). ADA was tapered and discontinued in another three patients in whom complete uveitis and arthritis inactivity

Table 1 Adalimumab treatment in patients with juvenile idiopathic arthritis (JIA)-associated uveitis

Patients receiving adalimumab treatment, *N* (%)	68 (17.6 %)
JIA subgroups	
- Oligoarthritis extended	40 (58.8 %)
- Oligoarthritis persistent	20 (29.4 %)
- Polyarthritis	8 (11.8 %)
Gender: male, female	14 (20.6 %), 54 (79.4 %)
ANA positive	58 (85.3 %)
RF positive	0
HLA-B27 positive	5 (7.3 %)
Anterior uveitis	68 (100 %)
Uni-, bilateral uveitis	11 (16.2 %), 57 (83.8 %)
Eye complications	
- Any	49 (72.1 %)
- Cataract	40 (58.8 %)
- Synechiae	39 (57.4 %)
- Band-keratopathy	31 (45.6 %)
- Ocular hypertension	12 (17.5 %)
- Glaucoma	9 (13.2 %)
- Macular oedema	3 (4.4 %)
- Dense vitreous opacity	1 (1.5 %)

Patient demographics and characteristics at start of adalimumab treatment

ANA antinuclear antibody, *RF* rheumatoid factor, *HLA-B27* human leucocyte antigen B27

had been maintained for at least 2 years (1.47 per 100 patient years).

In one other case, medication costs were no longer reimbursed by the patient's health insurance company and ADA therapy had to be stopped at 18 months of ADA treatment.

In four patients, ADA was discontinued due to side effects. These included lupus-like syndrome in one case (at 13 months of ADA treatment), and alopecia in another one (at 40 months). In one patient, drug was discontinued (at 64 months) owing to a non-malignant lymph-node hyperplasia and in another one (at 12 months) due to a combination of diverse side effects (distress, dizziness, vomitus, and headache).

In summary, ADA was discontinued in a total of 20 patients due to activity of uveitis ($n = 8$) or arthritis ($n = 4$), ≥2 years of complete disease inactivity ($n = 3$), drug cost reimbursement issues ($n = 1$) or adverse events ($n = 4$). Our data were underpowered for finding predictors for loss of treatment response (secondary failure).

Table 2 Adalimumab treatment in patients with juvenile idiopathic arthritis (JIA)-associated uveitis

Age at start of adalimumab (years, mean ± SD)	11.6 ± 4.5
Uveitis duration at start of adalimumab (years, mean ± SD)	6.3 ± 4.5
Conventional synthetic DMARDs, *N* (%)	68 (100 %)
- Methotrexate	52 (76.5 %)
- Azathioprine	12 (17.6 %)
- Cyclosporine A	10 (14.7 %)
- Sulphasalazine	1 (1.5 %)
- Leflunomide	1 (1.5 %)
- Mycofphenolate mofetil	1 (1.5 %)
Biological DMARDs, *N* (%)	8 (11.8 %)
- Etanercept	6 (8.8 %)
- Infliximab	2 (2.9 %)

Disease-modifying anti-rheumatic drugs (DMARDs) at baseline directly before the start of adalimumab treatment

Treatment after adalimumab discontinuation

After stopping ADA treatment, six patients were continued on the previous csDMARDs, and subsequent uveitis flares (in one of six patients) were treated with additional courses of corticosteroids. In another 14 patients, the treatment was switched to other biological drugs, namely to infliximab ($n = 6$), tocilizumab ($n = 3$), abatacept ($n = 2$), golimumab ($n = 1$), etanercept ($n = 1$) or rituximab ($n = 1$) (Table 3). Two of four patients who suffered severe adverse events probably related to ADA were switched to either tocilizumab or abatacept, and two continued with the previous csDMARD, namely methotrexate.

The treatment response to the drugs instituted after discontinuing ADA appeared to be rather heterogeneous, which at least in part may be influenced by the diverse

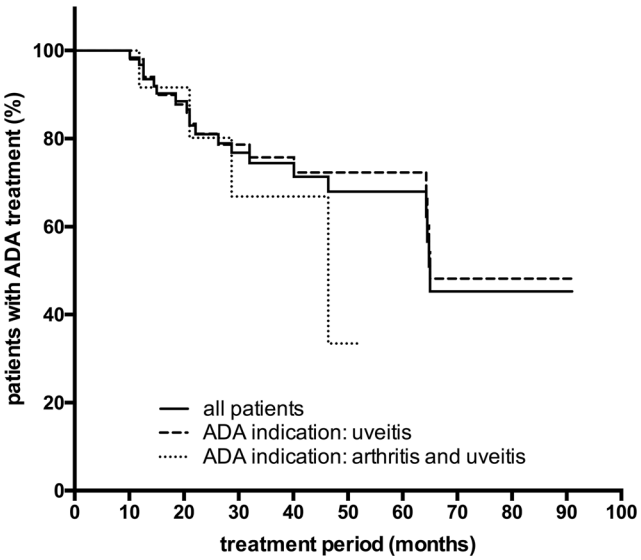

Fig. 2 Adalimumab treatment in patients with juvenile idiopathic arthritis-(JIA) associated uveitis. Kaplan-Meier curve describing probability of drug discontinuation in patients with primary response to adalimumab treatment ($N = 59$, *continuous line*). Furthermore, the subgroup of patients with ADA treatment indication of both active arthritis and uveitis (*dotted line*; ADA discontinuation in four patients) and the subgroup with treatment indication due to active uveitis alone (*dashed line*; ADA discontinuation in 16 patients) are shown. *x-axis*: treatment period in months. *Y-axis*: drug continuation probability

Table 3 Adalimumab treatment in patients with juvenile idiopathic arthritis (JIA)-associated uveitis

		Efficacy for uveitis	Efficacy for arthritis
Conventional synthetic DMARDs, *N* (%)	20 (100 %)		
– Methotrexate	15	11/15	10/15
– Azathioprine	2	1/2	1/2
– Leflunomide	2	0/2	2/2
– Mycophenolate mofetil	1	0/1	1/1
Biological DMARDs, *N* (%)	14 (70.0 %)		
– Etanercept	1	0/1	1/1
– Infliximab	6	3/6	5/6
– Golimumab	1	1/1	1/1
– Abatacept	2	1/2	1/2
– Tocilizumab	3	2/3	2/3
– Rituximab	1	1/1	1/1

Disease-modifying anti-rheumatic drugs (DMARDs) in 20 patients after discontinuation of adalimumab

combinations of csDMARDs and bDMARDs. In patients in whom ADA treatment response to uveitis was lost and who were subsequently switched to another biological agent, uveitis improved in eight, while inactivity could not be sustained in the others. In the four patients switched to another bDMARD for arthritis (all had uveitis inactivity), uveitis remained inactive in two of them, while eye disease recurred afterwards in the others.

Discussion

Despite the use of corticosteroids and csDMARDs, inactivity cannot be achieved in all patients with JIA and associated uveitis. Currently, TNF inhibitors are indicated at this disease stage to control disease and avoid subsequent complications, with ADA being the preferred drug. Our retrospective study supports previous reports that ADA is useful for the treatment of JIAU, as many of the patients showed a good response to treatment with this agent. As the duration of uveitis in our patients was already lengthy before starting ADA, we could only speculate as to whether an earlier use might have achieved even better response rates. However, the fact that none of our six patients, in whom ADA was already initiated within 12 months after disease manifestation, had revealed a treatment failure does support this notion.

Good treatment response of anti-TNF treatment was recently shown in a cross-sectional cohort in patients refractory to topical steroids and a second-line immunosuppressive agent [22]. Another study described that ADA was effective in JIA-associated uveitis in 88 % [19]. In 94 patients with immunosuppressive treatment-refractory JIA-associated uveitis, ADA improved activity in 28 % of patients, but activity worsened in 13 % of patients [23]. In 31 children with ANA-associated uveitis treated with TNF inhibitors for ≥2 years, uveitis inactivity was achieved in 71 % after 1 year and in 72 % after 2 years of treatment [24]. Of the twenty JIAU patients on ADA in another retrospective study, seven showed improvement, activity worsened in one, and no change was observed in uveitis activity in 12 [25]. In a further prospective interventional case series including 21 JIAU patients, inactivity was achieved with ADA in 29 out of 38 eyes at a mean follow-up of 18.2 months, and the flare rate was reduced [26]. In a study reporting the efficacy and safety of ADA for childhood non-infectious chronic uveitis, uveitis inactivity on ADA was seen in 12 out of 16 JIA patients. At 40 months on ADA, 60 % of children were still inactive [27]. In an Italian registry, the inactivity rate of JIAU with ADA treatment was 67.4 % ($n = 43$) [28]. In another multi-centre cohort study of JIA children treated with ADA, complete uveitis control was achieved in nine of ten patients [29]. In a multi-centre, prospective case series with JIAU ($n = 39$) refractory to standard immunosuppression, inflammation and macular thickness decreased significantly with ADA, and steroids could be tapered [30]. Finally, the current evidence for anti-TNF treatment effectiveness in childhood chronic uveitis was estimated in a systematic review and meta-analysis. In a pooled analysis of observational studies, the proportion of children responding to treatment was 87 % for ADA, 72 % for infliximab and only 33 % for etanercept [17]. The primary response rate of JIAU to ADA in our case series with 86.8 % clearly supports the previously reported high treatment response of this biological.

Nevertheless, the major focus of our study was to investigate the uveitis course during long-term ADA treatment. Our observations highlight the probability of loss of ADA treatment response for uveitis or arthritis, with the consequence of having to discontinue ADA after long-term treatment. Although attempted in this study, no clinical or laboratory predictive factors for loss of ADA treatment response and discontinuation could be found. Of the 31 patients on ADA from all eligible articles included in a previous meta-analysis, ADA was discontinued in two (6.5 %), notably due to lack of

effectiveness in one and adverse events in another [17]. In another retrospective study including 20 JIAU patients, six patients (30 %) discontinued ADA during the follow-up because lack of treatment response and one (5 %) because of inactive uveitis [25].

Uveitis reactivation after withdrawing ADA was rarely observed in our patients, but it does probably increase in the long term. In a recent study, the reactivation of childhood uveitis following discontinuation of TNF inhibitors was studied. Amongst those patients on anti-TNF who discontinued treatment, the likelihood of reactivation was higher for those on ADA than on infliximab [31]. In our study, ADA was discontinued ≥2 years of complete uveitis inactivity in three cases (1.47 per 100 patient-years). In one of three of these patients, uveitis became reactivated after 6 months.

A previous study reported that switching to a second anti-TNF inhibitor in children with autoimmune uveitis improved uveitis in 75 % of the cases. Eleven of the 17 patients on etanercept and all of the 23 on infliximab were switched to ADA [17]. Nevertheless, in our patients in whom ADA treatment response was lost and the drug then discontinued, treatment was switched to other biological agents or csDMARDs. Alternatively, other TNF inhibitors (etanercept, infliximab or golimumab), anti-IL-6R (tocilizumab), blockade of T-cell activation (abatacept), or B-cell depletion via anti-CD-20 (rituximab) treatment strategies were used. The choice of medication was influenced by the current pathogenetic knowledge of disease, preferred pattern of practice, patient comorbidities, and also probable adverse events.

In a previous study, the efficacy of ADA for childhood uveitis when used as the first anti-TNF therapy versus ADA after a previous infliximab has failed was compared. Once uveitis inactivity was achieved, the time to first relapse was significantly longer when ADA was used as the first biological than when ADA was used after a previous infliximab had failed (18 versus 4 months) [29]. The treatment response of the biologicals given to our patients as alternative agents to ADA could have been affected similarly.

In a recent study, adverse events in JIA patients included in a prospective registry were noted in 7.9 % out of 289 patients [32]. In another safety evaluation of 348 consecutive patients treated with biological agents in three tertiary centres in Finland, the most common adverse events were infections. The rate of serious adverse events on adalimumab was 10.1/100 patient-years [33].

In conclusion, ADA is useful for the treatment of patients with JIAU. As its effect may decline during long-term treatment, further treatment options are needed. Predictive factors for response to treatment and for its failure, and also guidance for immunomodulatory therapy are urgently needed. Therefore, basic and clinical research on JIA-associated uveitis should be intensified.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Ethical approval This study was conducted as a retrospective trial. For this type of study formal consent is not required.

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