EXTENDED REPORT

Retention time for corticosteroid-sparing systemic immunosuppressive agents in patients with inflammatory eye disease

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Background: Multiple immunosuppressive drugs have been used to manage inflammatory eye disease when control cannot be achieved by corticosteroid alone. However, although clinical studies support the effectiveness of most of these agents, comparative studies have not been undertaken. Retention time, a measure of the duration of treatment with any given drug, is a crude indicator of drug effectiveness and tolerability that facilitates such a comparison. The retention time was compared for corticosteroid-sparing immunosuppressive agents in patients attending our tertiary referral inflammatory eye disease clinic.

Methods: The clinical records of all patients attending an inflammatory eye disease clinic at the Casey Eye Institute over a 1-year period (2003) were reviewed. From these records, we collected the following clinical data: age; sex; ocular diagnosis; and use of steroid-sparing systemic immunosuppression, including drugs, duration of treatment and, if ceased, reasons for cessation. Cox regression analysis, adjusted for clustering, was used to compare other drugs against methotrexate.

Results: 107 of 302 (35%) patients seen at the inflammatory eye disease clinic in 2003 had a total of 193 current or past prescriptions for systemic steroid-sparing immunosuppressive agents. The treated group, most of whom had uveitis, included 32 men and 75 women, aged 5-86 years. Most commonly prescribed were methotrexate (66 uses, 34%), ciclosporin (37 uses, 19%), azathioprine (26 uses, 13%), mycophenolate mofetil (22 uses, 11%) and cyclophosphamide (15 uses, 8%). Patients were retained significantly less on ciclosporin ($p=0.004$), azathioprine ($p=0.04$), mycophenolate mofetil ($p=0.04$) and cyclophosphamide ($p<0.001$) compared with methotrexate. Reasons for cessation included adverse events, lack of effectiveness, success or remission, cost and desire for fertility.

Conclusions: In patients with inflammatory eye disease, methotrexate may offer a superior combination of effectiveness and tolerability over other commonly used corticosteroid-sparing immunosuppressive agents. In this study, there was a twofold risk of not being retained on azathioprine, mycophenolate mofetil and ciclosporin and a fourfold risk of not being retained on cyclophosphamide compared with methotrexate.

Multiple corticosteroid-sparing immunosuppressive agents have been used to treat immune-mediated forms of inflammatory eye diseases, including uveitis, scleritis and orbital inflammatory disease, when vision is threatened, and either the patient cannot tolerate oral prednisone or the disease cannot be controlled. Case series and controlled clinical trials support the use of most of these drugs, but comparative studies, particularly between different classes of drugs, are lacking.¹⁻¹⁵ Although nowadays the concept of evidence-based medicine recommends that a doctor's decision making should be based on the results of randomised controlled clinical trials,¹⁶ such studies are rare in the specialty of inflammatory eye disease.¹⁷ Barriers include the low incidence of these disorders, the heterogeneity of each disease and the lack of validated diagnostic criteria for many subtypes, as well as the high cost of several of these drugs. Consequently, other legitimate methods for differentiating between an ever-increasing number of "conventional" and "biologic" immunosuppressive drugs are required.

In several other medical disciplines, "retention time" has been used to compare drug effectiveness and toxicity.¹⁸⁻²⁰ In essence, the retention time for any given drug, also variously referred to as drug "persistence", "survival" or "discontinuation rate", refers to the time a patient continues to take that drug. When considering treatment of chronic diseases, retention time provides a measure of drug effectiveness and

tolerability. Although comparing retention times for different drugs used for the same indication seems to be a rather simplistic approach, it has become an accepted method to assess the relative effectiveness of drugs used for chronic diseases. For example, the measurement of retention time has helped to establish the relative value of ocular hypotensive treatments in glaucoma, as reported in supplements to the *American Journal of Ophthalmology* (supplement to volume 137, 2004) and the *American Journal of Managed Care* (supplement to volume 8, 2002). In addition, and of particular relevance to inflammatory eye disease, the measure has been used by rheumatologists to distinguish between disease-modifying antirheumatic drugs for rheumatoid arthritis.^{21, 22}

In this study, we compared the retention time for corticosteroid-sparing systemic immunosuppressive agents used to manage inflammatory eye disease. As it was our clinical impression that methotrexate was well tolerated and presented an excellent safety profile, we hypothesised that methotrexate would have a longer retention time than other immunosuppressive agents that we commonly prescribed.

METHODS

All patients who, during 2003, attended a weekly clinic at the Casey Eye Institute (Portland, Oregon, USA) for the management of inflammatory eye diseases were enrolled in a

retrospective study of retention time on corticosteroid-sparing systemic immunosuppressive agents. At this clinic, steroid-sparing systemic immunosuppression is prescribed and monitored in accordance with the guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders.²³ Medical charts of all patients were examined to collect prespecified demographic and clinical information that included age; sex; ophthalmological diagnosis and, in the case of uveitis, disease subtype; corticosteroid-sparing immunosuppressive treatments including dates on which a drug was started and, if applicable, ceased; and if any drug had been discontinued, reason for cessation. Charts were analysed retrospectively, and start and cessation dates for all instances of corticosteroid-sparing immunosuppressive treatments were noted for each patient. Many patients received more than one drug, and follow-up information extended as long as 5000 days. If patients were still on one or more drugs at the time that we began data collection (30 June 2004), they were recorded as continuing on the drugs for the purposes of the statistical analysis. Patients who were enrolled in clinical trials at any time during their period of attendance at the clinic were not included in this study to avoid the possibility that time of receiving drugs was dictated by a study protocol. The institutional review board gave approval for this study.

STATISTICAL ANALYSES

Data were entered into Stata statistical software. Six potential patients were removed from subsequent analyses because they had not been re-evaluated clinically after starting the relevant drug, at the time we began data collection. Retention time for the usage of each drug was calculated by subtracting the date the drug was started from either the date the drug was discontinued (for any reason) or the date that the patient was last reviewed by a clinician. Frequencies for relevant clinical and demographic data were calculated. Survival analyses (Kaplan–Meier method and Cox proportional hazards regression model) were undertaken, as these methods allow for variable lengths of follow-up and account for different end points. Kaplan–Meier survival plots were constructed to allow visual representation of retention (survival) time for the five most common drugs. Median retention times were estimated using the Kaplan–Meier method for each of these five drugs. Cox regression analyses were conducted to assess whether retention time was significantly different between the five most commonly prescribed drugs. In these analyses, methotrexate was set as the comparison agent.

All analyses were adjusted for clustering by subject, because many patients had trials of more than one drug during the study period. Three separate models were developed: (a) all ophthalmological diagnoses and all reasons for drug cessation were included; (b) only data from patients with uveitis were included; and (c) all diagnoses were included, but drug usages where cessation occurred because the underlying disease was considered to have remitted were excluded. These usages were not included because ceasing treatment due to lack of effectiveness or side effects is quite different to discontinuing treatment because disease has remitted.

RESULTS

A total of 302 people attended a weekly clinic (with JTR) at the Casey Eye Institute's inflammatory eye disease service on one or more occasions during 2003. Of these 302 people, 113 patients had a history of taking one or more non-corticosteroid systemic immunosuppressive drugs and had never been enrolled in a clinical trial of such treatment. As noted above, six potentially eligible patients had not had a subsequent

Table 1 Characteristics of the study sample (n = 107)

Variable	No of patients (%) or mean (SD)
Age (years)	49 (17.6); range 5–86
Sex	
Male	32 (30%)
Female	75 (70%)
Ophthalmological diagnosis	
Uveitis	69 (64%)
Scleritis/episcleritis/keratitis/corneal melt	24 (22%)
Orbital inflammatory disease	8 (7%)
Optic neuritis	3 (3%)
Other	3 (3%)
Uveitis subtype (n = 69)	
Non-classifiable	26 (38%)
HLA B27-associated	7 (10%)
Pars planitis	6 (9%)
Retinal vasculitis	5 (7%)
Juvenile rheumatoid arthritis	4 (6%)
Sarcoidosis	4 (6%)
Behçet's syndrome	3 (4%)
Birdshot retinochoroidopathy	3 (4%)
Multifocal choroiditis	2 (3%)
Blau's syndrome	2 (3%)
Serpiginous choroidopathy	2 (3%)
Other	5 (7%)

HLA, human leucocyte antigen.

clinical visit at the time of data collection and were thus excluded from further analyses. Thus, data from 107 patients remained for inclusion in this study. Table 1 summarises the demographic and clinical data collected on these patients.

The number of uses of immunosuppressive drugs totalled 193 in the 107 participants. Table 2 gives a description of the number of uses of each specific drug, along with the median length of retention of patients prescribed the most commonly used drugs. Figure 1 shows the Kaplan–Meier survival curves for the five most commonly prescribed drugs (ie, methotrexate, ciclosporin, azathioprine, mycophenolate mofetil and cyclophosphamide). Visual inspection of these curves suggests that although there is little difference in survival (retention) between azathioprine, mycophenolate mofetil, ciclosporin and cyclophosphamide, methotrexate appears to be associated with greater retention than the other drugs. This was subsequently tested with Cox regression analyses.

No significant relationship was found between retention probability and sex ($p=0.2$) or age ($p=0.1$) by Cox regression analysis using patients on all possible drugs. In

Table 2 Number of uses of each specific drug treatment (number of observations = 193, n = 107)

Treatment	No of uses of drug (%)	Median retention time* (days)
Methotrexate	66 (34)	1216
Ciclosporin	37 (19)	426
Azathioprine	26 (13)	303
Mycophenolate mofetil	22 (11)	274
Cyclophosphamide	15 (8)	487
Etanercept	8 (4)	NA
Sulfasalazine	7 (4)	NA
Infliximab	6 (3)	NA
Leflunomide	2 (1)	NA
Intravenous immunoglobulin	2 (1)	NA
Chlorambucil	1 (0.5)	NA
Interferon	1 (0.5)	NA
Total	193 (100)	578

NA, not available because numbers of drug users were too small to give a standard distribution.

*Defined as the time from which the drug was started to either cessation of drug or end of the study period.

Figure 1 Kaplan-Meier survival curves showing probability of being retained on drug versus total analysis time at risk, for all ophthalmological diagnoses ($n = 101$, number of observations = 166).

98 of the 193 drug treatments, drugs were ceased, giving an overall percentage of discontinuation of 51%. Reasons for cessation of drug were lack of effectiveness ($n = 35$), adverse events ($n = 25$), disease remission or treatment success ($n = 13$), poor compliance ($n = 5$), cost ($n = 2$), other reasons ($n = 4$) and multiple reasons ($n = 9$); in five instances, reasons for cessation were not specified in the medical records. Table 3 provides the information on reasons for cessation of drugs.

The first Cox regression analysis included 101 patients treated with one or more of the five most commonly prescribed drugs, regardless of diagnosis or reason for drug cessation. This analysis, presented in table 4, showed that patients were retained for a significantly shorter time on ciclosporin ($p = 0.004$), azathioprine ($p = 0.04$), mycophenolate mofetil ($p = 0.04$) and cyclophosphamide ($p = 0.001$) compared with methotrexate. There was an increase in the risk of not being retained on a drug compared with not being retained on methotrexate of approximately twofold for ciclosporin, azathioprine and mycophenolate mofetil, and approximately fourfold for cyclophosphamide. Table 5 shows the analysis, repeated for 63 patients diagnosed with uveitis only, which gave similar results. Finally, because it was possible that our results were biased by including patients who discontinued a drug because of disease remission, we repeated the Cox regression analysis excluding the 15 patients who had ceased treatment with the drug for this reason (including two patients classified as ceasing treatment with the drug for multiple reasons), and found that

methotrexate continued to show a more favourable retention rate (table 6).

DISCUSSION

We investigated the retention time for methotrexate versus other corticosteroid-sparing systemic immunosuppressive agents conventionally used to treat inflammatory eye disease in a cohort of 107 patients attending one doctor's clinic over a 1-year period. Our hypothesis that methotrexate had a relatively longer retention time, implying a superior combination of effectiveness and tolerability over other agents, was confirmed by Cox regression analysis adjusted for clustering. The analysis showed that patients were twice as likely to stop other antimetabolites, azathioprine and mycophenolate mofetil, and the T cell modulator, ciclosporin, and four times as likely to stop the alkylating agent, cyclophosphamide, compared with methotrexate. A similar result was obtained when the analysis was repeated including patients with uveitis only. Finally, because it is common practice to attempt to wean patients from immunosuppression if disease has been quiescent for 6–12 months, we repeated the analysis excluding patients who ceased the drug owing to remission of disease. Despite a smaller sample size, all drugs were significantly less likely to be retained compared with methotrexate.

Methotrexate, an antimetabolite that targets rapidly dividing leucocyte precursors by inhibiting DNA replication at the level of dihydrofolate reductase, has a therapeutic history dating back to the 1950s, originally as a treatment for cancer but later also in inflammatory diseases.²⁴ In agreement with our findings, studies from the rheumatological literature

Table 3 Reasons for cessation of drugs (number of times drugs were discontinued = 98)

Reason	No of times drugs were discontinued (%)
Lack of efficacy	35 (36)
Adverse events	25 (26)
Success or remission	13 (13)
Multiple reasons*	9 (9)
Poor compliance	5 (5)
Not specified in case notes	5 (5)
Miscellaneous reasons	4 (4)
Cost	2 (2)
Total	98 (100)

*Includes two participants where one of the "multiple reasons for cessation" included remission of disease.

Table 4 Cox regression model comparing retention time between methotrexate, and azathioprine, mycophenolate mofetil, ciclosporin and cyclophosphamide for patients with all ophthalmological diagnoses ($n = 101$, number of observations = 166, number of times drugs were discontinued = 90)

Treatment	HR	SE	p (95% CI)
Ciclosporin	2.19	0.593	0.004 (1.28 to 3.72)
Azathioprine	2.00	0.683	0.04 (1.02 to 3.90)
Mycophenolate mofetil	2.29	0.899	0.04 (1.06 to 4.94)
Cyclophosphamide	4.31	1.119	0.001 (2.59 to 7.17)

Adjusted for clustering on subject.

Table 5 Cox regression model comparing retention time between methotrexate, and azathioprine, mycophenolate mofetil, ciclosporin and cyclophosphamide for patients with a diagnosis of uveitis only (n = 63, number of observations = 104, number of times drugs were ceased = 53)

Treatment	HR	SE	p (95% CI)
Ciclosporin	2.61	0.800	0.002 (1.43 to 4.76)
Azathioprine	2.41	1.147	0.07 (0.95 to 6.12)
Mycophenolate mofetil	2.69	1.453	0.07 (0.93 to 7.76)
Cyclophosphamide	7.01	2.951	0.001 (3.07 to 16.00)

Adjusted for clustering on subject.

indicate a prolonged retention time of methotrexate, in patients with rheumatoid arthritis. Pincus *et al*²¹ studied 532 patients attending seven private rheumatological practices in the US and found that methotrexate was continued significantly longer than other second-line drugs that included azathioprine, gold, hydroxychloroquine and penicillamine. Aletaha and Smolen²² investigated the use of disease-modifying antirheumatic drugs in 593 patients from two hospital rheumatology clinics in Vienna. They found that of single-agent treatments, patients were retained on methotrexate longer than all other drugs, including ciclosporin, sulfasalazine, gold, chloroquine and penicillamine, with the exception of azathioprine. As well as reports of effectiveness for inflammatory eye disease,¹⁻³ methotrexate has the reputation of being well tolerated. As discussed by an expert panel on management of inflammatory eye disease,²³ the most common side effect is gastrointestinal disturbance; often, this is alleviated by combination with folic acid or giving the drug subcutaneously. Bone-marrow suppression, cirrhosis and interstitial pneumonitis are serious complications that fortunately occur infrequently. Other factors that could contribute to patient continuation on methotrexate include the relatively low cost of this agent in comparison with other non-corticosteroid immunosuppressive agents and once-weekly frequency of administration.

Although patients were retained on methotrexate for a considerable length of time, our data paint a disappointing picture of systemic immunosuppressive treatment for inflammatory eye disease. Overall, 51% of drugs were discontinued, and approximately two thirds of patients stopped for lack of effect or side effects. This result agrees with the comprehensive report of systemic drug toxicity trends by Tamesis *et al*,²⁵ who found that drugs including methotrexate, azathioprine, ciclosporin, cyclophosphamide and chlorambucil were continued by just 32–45% of patients with various ocular inflammatory syndromes. Newer agents promise longer retention times. Two recent large studies suggest that mycophenolate mofetil may be very effective and safe for inflammatory eye disease, although follow-up in both studies is limited. Thorne *et al*⁵ described a group of 84 patients

treated with mycophenolate for inflammatory eye disease, with a median follow-up of 10 months; the drug was discontinued for ineffectiveness and side effects in approximately 10% and 8% of patients, respectively. Siepmann *et al*¹⁶ have followed a cohort of 106 patients with uveitis taking mycophenolate for at least 6 months, with just four treatment failures and no side effects requiring cessation of drug. Our experience with mycophenolate is less positive, but our impressions are based on only 22 patients. New biologic agents that specifically target key molecules in inflammatory signalling pathways are attracting much attention in our field. In particular, blockade of tumour necrosis factor α with the monoclonal antibody, infliximab, has been heralded as highly effective for patients with recalcitrant uveitis. However, recent work from our group¹⁴ indicates that retention time is short, owing to the frequent occurrence of treatment-limiting side effects.

Our data suggest that methotrexate offers a favourable combination of tolerability and effectiveness for the treatment of uveitis and inflammatory eye disease in general. Our study is limited by the small size of the study cohort and retrospective data collection. In addition, we are studying a heterogeneous collection of diseases. Specific subsets of uveitis, such as Behçet's disease or serpiginous choroidopathy, might respond preferentially to a given drug, thus extrapolating from an analysis based on all patients with uveitis could fail to identify the utility of a specific drug for a defined subset. Our data are derived from a single clinical practice, which introduces unavoidable bias relating to the drug preference of the prescribing doctor. If we routinely prescribe methotrexate as the preferred corticosteroid-sparing agent, we might selectively place those patients who are best able to tolerate immunosuppression and artificially extend the retention time for this drug. Although we cannot deny our enthusiasm for methotrexate, the underlying philosophy of the clinic is to take an individualised approach when selecting a corticosteroid-sparing immunosuppressive, considering specifics of the ocular inflammatory disease, medical history and lifestyle factors, including the wish to consume alcohol, which would relatively contraindicate methotrexate. It is obvious from our data that a wide range of immunosuppressive drugs are prescribed in this clinic.

Although our study was not designed to assess quality of life, another way of assessing differences in effectiveness of drugs is to collect of quality of life data, which includes measurements of the effect of disease on physical, social and psychological well-being. Particularly when drugs are extremely expensive, if quality of life is shown to be enhanced, arguments can be made for funding on the basis of appropriate cost-utility analyses. Future studies on the effectiveness of corticosteroid-sparing systemic immunosuppressive agents could be strengthened by including measurement of quality of life.

This work shows the use of the concept of retention time to evaluate and compare different drug treatments for

Table 6 Cox regression model comparing retention time between methotrexate, and azathioprine, mycophenolate mofetil, ciclosporin and cyclophosphamide for patients with all ophthalmological diagnoses, but excluding patients who discontinued drug due to disease remission (n = 92, number of observations = 151, number of times drugs were discontinued = 75)

Treatment	HR	SE	p (95% CI)
Ciclosporin	2.25	0.65	0.005 (1.28 to 3.95)
Azathioprine	3.01	1.26	0.009 (1.32 to 6.86)
Mycophenolate mofetil	2.19	0.86	0.046 (1.01 to 4.72)
Cyclophosphamide	4.84	1.50	0.001 (2.63 to 8.90)

Adjusted for clustering on subject.

inflammatory eye disease. Given the difficulties that have hindered randomised controlled clinical trials in this field to date, there is much value to such an approach, particularly if prospectively collected data are pooled from multiple clinical centres over a defined time. In this way, the effectiveness and tolerability of both conventional and novel drugs, singly or in combination, could be evaluated.

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