

SCIENTIFIC CORRESPONDENCE

Suspension of anticytomegalovirus maintenance therapy following immune recovery due to highly active antiretroviral therapy

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Abstract

Aim—To describe the authors' experience with discontinuation of anti-cytomegalovirus (CMV) maintenance therapy in patients showing immune recovery following highly active antiretroviral therapy (HAART).

Methods—Retrospective analysis of the records of 41 patients who presented with CMV retinitis and whose maintenance therapy was discontinued from March 1997 to December 1999.

Results—41 patients had their anti-CMV therapy discontinued. The mean follow up after discontinuation of maintenance therapy in April 2000 was 20.4 months. At the time of discontinuation of maintenance therapy the lowest CD4+ count was 143 cells $\times 10^6/l$ and only three patients had detectable HIV viral load. No reactivation or progression was seen in any of these patients after suspension of maintenance therapy.

Conclusion—The anti-CMV maintenance therapy could be discontinued safely in patients with CD4+ above 150 cells $\times 10^6/l$ although close follow up remains necessary especially in patients whose CD4+ count drops below this level.

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therapy leads to an increase in CD4+ counts and a control of HIV replication resulting in decrease of viral load. As the development of CMV retinitis is directly linked to CD4+ counts and host immunity, the increase in the CD4+ count itself may lead to control of the disease without specific therapy. Based on this, some authors have attempted discontinuation of maintenance anti-CMV therapy for those patients who have shown immune recovery; however, the level of recovery at which this could be safely done has not yet been clearly defined.³⁻⁵

The goal of this paper was to describe the authors' experience with the discontinuation of maintenance anti-CMV therapy and to discuss when therapy could be stopped safely.

Patients and methods

The authors reviewed the records of HIV positive patients who had CMV retinitis, and whose maintenance therapy had been discontinued, between March 1997 and December 1999. Forty one patients had their anti-CMV therapy discontinued. Patients were considered for discontinuation of maintenance anti-CMV treatment if they were on HAART and had shown an increase of their CD4+ above 100 cells $\times 10^6/l$ in one single test, and had an undetectable HIV viral load, which was regarded as a good response to HAART. The duration of HAART therapy before discontinuation of anti-CMV therapy was not taken into consideration. These parameters (CD4+ counts and HIV viral load) were monitored every 3 months. All patients were examined by indirect ophthalmoscopy after pupillary dilatation every 2 weeks. The final data analysis was considered in April 2000.

Results (Table 1)

Out of 41 patients 33 (80.5%) were male and eight (19.5%) female. The mean age was 35.5 years ranging from 22 to 56. Thirty one (75.6%) patients had bilateral disease and 10 (24.4%) unilateral, reaching a total of 72 affected eyes.

At the time of the diagnosis of CMV retinitis the mean CD4+ counts was 44.6 cells $\times 10^6/l$ (range 3-102, median 42). The mean duration of CMV retinitis treatment was 20.4 months

Cytomegalovirus (CMV) retinitis is the most common ocular infection in HIV positive patients and usually affects patients with very low CD4+ counts.¹ There are many modalities of treatment for CMV, including intravenous, intraocular, and oral therapy. The control and reactivation of the disease depend on the anti-CMV drug and routes of delivery used vary. The treatment for CMV retinitis is usually divided into two phases—induction and maintenance. Until recently discontinuation of maintenance therapy was not a possibility since the drugs are virustatic and treatment against HIV infection was unable to improve the patient immune status.

After the introduction of HAART (highly active antiretroviral therapy) some clinical features of CMV retinitis have changed due to immune recovery.² This potent anti-HIV

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Table 1 Patient characteristics and treatment

Patient No	Age	CD4+ count at CMV DX	Initial CMV therapy	Duration of CMV therapy (months)	CD4+ count when CMV therapy stopped	HIV viral load when CMV therapy stopped	Follow up since CMV therapy stopped (months)	Duration of HAART before CMV therapy	CD4+ count at last visit
1	35	27	IV GCV	36	326	UND	24	23	675
2	41	65	IV GCV	8	235	UND	30	7	483
3	43	12	IV GCV	32	212	UND	33	15	296
4	28	11	IV GCV	17	262	UND	22	18	821
5	39	25	IV GCV	36	318	UND	22	21	798
6	27	3	IV GCV	39	449	UND	24	20	806
7	56	62	IV GCV	29	274	UND	27	22	383
8	38	31	IV GCV	16	306	UND	29	16	402
9	33	7	IV GCV	41	295	UND	18	31	493
10	34	43	IV GCV	30	273	UND	27	22	286
11	34	46	IV GCV	30	273	UND	27	21	461
12	47	54	IV GCV	19	238	UND	26	19	819
13	45	102	IV GCV	7	296	UND	21	6	360
14	37	76	IV GCV	8	231	UND	31	7	292
15	37	12	IV GCV	31	274	UND	20	29	323
16	37	95	IV GCV	8	297	UND	31	7	450
17	41	6	IV GCV	24	216	UND	22	22	427
18	39	18	IV GCV	25	287	UND	23	25	545
19	36	6	IV GCV	23	347	UND	30	19	738
20	29	86	IV GCV	11	295	UND	19	15	463
21	28	96	IV GCV	17	286	UND	19	21	374
22	34	35	IV GCV	13	219	UND	21	5	296
23	29	25	IV GCV	18	379	UND	21	11	542
24	30	55	IV GCV	7	275	UND	21	8	293
25	22	n/a	IV GCV	38	304	230	14	13	581
26	38	27	IV GCV	41	489	321	14	28	872
27	37	8	IV GCV	21	184	UND	37	7	422
28	39	26	IV GCV	43	176	UND	24	20	506
29	27	87	IV GCV	16	163	UND	21	17	285
30	31	36	IV GCV	22	169	UND	22	13	618
31	36	32	IV GCV	15	158	UND	18	6	373
32	34	45	IV GCV	11	156	UND	21	8	747
33	31	27	IV GCV	9	149	UND	18	7	216
34	39	62	IV GCV	25	152	UND	17	11	181
35	41	74	IV GCV	9	185	UND	5	9	335
36	33	46	IV GCV	11	171	UND	7	10	562
37	38	65	IV GCV	9	146	UND	6	9	268
38	35	73	IV GCV	10	162	UND	6	10	194
39	32	41	IV GCV	10	181	UND	7	9	308
40	37	71	IV GCV	9	168	UND	7	13	452
41	28	67	IV GCV	13	143	UND	6	8	312
Mean	35.5	44.6		20.4	246.8	275.5	20.4	14.8	464.8
Maximun	56	102		43	489	321	37	31	872
Minimum	22	3		7	143	230	5	5	181
Median	36	42		17	238	275.5	21	13	427

CMV = cytomegalovirus retinitis; IV GCV = intravenous ganciclovir; HAART = highly active antiretroviral therapy; UND = undetectable.

(range 7–23, median 17). All patients were initially treated with intravenous ganciclovir. Two (4.8%) patients had an intraocular sustained release device of ganciclovir (Vitaset, Chiron Vision) implanted. After 6 months one (2.4%) of these patients was put back on intravenous ganciclovir and the other was not put on any other form of anti-CMV treatment. Five (12.2%) patients presented with one episode of reactivation of the retinitis during maintenance treatment and were treated with intravenous ganciclovir at induction levels. After good response to HAART therapy the patients had their anti-CMV maintenance therapy discontinued. The mean CD4+ count at this time was 246.8 cells $\times 10^6/l$ (range 143–489, median 238) and only two (4.8%) patients showed detectable HIV viral load. The mean duration of HAART was 14.8 months (range 5–31, median 13). The mean duration of follow up after discontinuation of therapy and April 2000 was 20.4 months (range 5–37, median 21). Eleven (26.8%) patients had been followed for more 24 months, 23 (56.1%) between 12 and 24 months, and seven (17.1%) for less than 12 months. Eight patients (19.5%), 13 eyes, with inactive retinitis developed cystoid macular

oedema (CMO) secondary to immune recovery. All patients who presented with CMO initially presented with peripheral CMV retinitis. One patient (2.4%) presented with unilateral optic disc neovascularisation. The mean CD4+ count at last assessment was 464.8 cells $\times 10^6/l$ (range 181–872, median 427). No reactivation or progression of the retinitis was seen in any of these patients after discontinuation of the maintenance therapy.

Discussion

Since the advent of HAART many authors have shown that anti-CMV maintenance therapy could be discontinued following immune recovery.^{3–5} CD4+ counts, HIV viral load, and CMV viraemia are the factors that have been most frequently used to monitor immune recovery.⁶ In our retrospective study of 41 patients who had their anti-CMV therapy discontinued following good response to HAART, all patients had CD4+ counts above 100 cells $\times 10^6/l$ and only two patients had detectable HIV viral load at the time therapy was stopped. Even though an undetectable

HIV viral load had been established as a minimal requirement for discontinuation of anti-CMV therapy, these two patients requested interruption of their treatment following CD4+ increase.

The level of recovery (CD4, HIV viral load) at which anti-CMV therapy can be safely discontinued is still debatable. Authors have considered CD4+ counts above 100 cells $\times 10^6/l$ as safe for stopping anti-CMV therapy.³ Macdonald *et al* considered CD4+ counts above 50 cells $\times 10^6/l$ for 3 months to discontinued anti-CMV therapy, although in their series only two presented with CD4+ counts below 100 cells $\times 10^6/l$.⁷ This result does not support a recommendation for discontinuation of therapy below 100 cells $\times 10^6/l$. Even though there are a few cases in which CMV retinitis relapsed in spite of a higher CD4+ count, this factor remains as the single most important to be considered when deciding to discontinue maintenance therapy.⁸ The proliferation of specific clones of anti-CMV T lymphocytes may be important in the control of the retinal infection, and this has been demonstrated by a study which showed that the presence of active end organ disease had a strong correlation with loss of CMV specific lymphocyte response.⁹ The same authors state that this specific immune recovery was stimulated by HAART.⁹ Unfortunately this kind of test is not practical in the clinical setting, and our data, and those of others, do not support its regular use. However, it may become useful in situations where discontinuation of anti-CMV therapy is to be attempted in someone with a CD4+ count lower than 150 cells $\times 10^6/l$.

Song *et al* demonstrated that a decrease of CD4+ cells below 50 cells $\times 10^6/l$ following HAART failure increased the risk of CMV retinitis reactivation, and that the increase in the HIV viral load was not predictive of reactivation. This value of 50 cells $\times 10^6/l$ has been shown to be important both for the development and the reactivation of CMV retinitis. They also stated that even though the maintenance therapy can be discontinued there is no guarantee that CMV retinitis will not relapse and that these patients should be followed closely, especially those showing failure with HAART.¹⁰ In our study, none of the patients showed reactivation of CMV retinitis after a mean follow up of 20.4 months, with over 50% of them having been followed for over 1 year, including those patients who had detectable HIV viral load. None of our patients presented with CD4+ counts at the last assessment below the level at which they had their anti-CMV therapy stopped.

The mean CD4+ count at the time of diagnosis of CMV retinitis, and the duration of CMV retinitis did not seem to influence recovery and do not represent risk factors for reactivation of CMV retinitis following HAART. History of previous relapses during maintenance therapy, requiring re-induction therapy, also did not seem to represent a risk factor for poor response.

Mitchell *et al* demonstrated that patients responsive to HAART within 3 months and previous CMV retinitis did not show reactivation of the disease.¹¹ All patients in our study had been on HAART for at least 5 months when anti-CMV therapy was discontinued, even though the duration of HAART was not considered as a criterion for discontinuation of therapy.

Whitcup *et al* in a prospective study found that patients with CD4+ counts above 150 cells $\times 10^6/l$ could have their anti-CMV maintenance therapy discontinued safely.¹² In our study, even though the criterion for discontinuation had been established at 100 cells $\times 10^6/l$ only three patients had a value lower than 150 cells $\times 10^6/l$. These data only allow us to conclude that levels above 150 cells $\times 10^6/l$ are safe. Only a much larger number of individuals with lower counts will allow us to make a different recommendation. Another important aspect to be considered is related to the fact that this decision about CD4 count level was made around 3 years ago, at a time when nearly no data were available on this subject. The level of 100 cells $\times 10^6/l$ was considered to be a reasonable level at that time, and until now there are no convincing data that lower levels are safe. Close follow up of these patients remains necessary, especially when CD4+ count drops below this established level.

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