CASE REPORT

Montelukast in the treatment of HIV associated immune reconstitution disease

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The pathogenesis of immune reconstitution disease (IRD) is not well understood and it can be difficult to manage. Leukotrienes exert proinflammatory effects, have an important role in the innate immune response, and are relatively deficient in HIV infection. Montelukast is a leukotriene receptor antagonist (LTRA) currently licensed for the treatment of asthma. We report a series of three patients with severe HIV associated IRD (cases 1 and 2 associated with starting HAART and unresponsive to steroids), who obtained clinically dramatic responses to treatment with montelukast. The first case is of IRD to secondary syphilis and the second and third to tuberculosis. Cases 1 and 3 both relapsed after a temporary break from montelukast and resolved on restarting. Montelukast should be considered in HIV associated IRD as an alternative to steroids and where these are not effective. Leukotriene overactivity may be implicated in IRD.

Immune reconstitution disease (IRD) to a variety of organisms occurs frequently on starting highly active anti-retroviral therapy (HAART) at a low CD4 count. It is also described in the absence of HIV infection after commencing tuberculosis treatment (paradoxical reaction). We report three patients with severe HIV associated IRD who had dramatic responses to treatment with montelukast. All three patients gave their informed consent to the use of montelukast for this unlicensed indication.

CASE 1

A 36 year old man was started on HAART after a year off treatment (see table 1). Eight weeks previously he had developed a generalised maculopapular rash which became psoriaform and was accompanied by fever. Two months after restarting HAART the rash became urticarial. During this time he had also developed rhinitis and iritis.

Intensive inpatient investigation failed to find a cause of his rash and fever until syphilis serology, previously repeatedly negative, became strongly positive. Before this diagnosis he had received 4 weeks of high dose flucloxacillin for a staphylococcal septicaemia and clarithromycin for 6 weeks as empirical treatment for *Mycobacterium avium intracellulare* complex. He was subsequently formally treated for syphilis with 17 days of procaine penicillin.

Despite antibiotics his urticarial rash and fever showed no improvement with oral steroids, antihistamines, or ranitidine. Montelukast (Singulair, MSD) 10 mg daily was started. Within 24 hours the fever settled and the rash started to resolve. His symptoms recurred on stopping montelukast on two occasions, 2 months and 3 months after initiation. He finally stopped montelukast after 5 months of treatment without symptomatic relapse.

We think that the maculopapular rash, iritis, and rhinitis were caused by secondary syphilis and that the urticarial rash was the result of IRD to syphilis.

CASE 2

A 41 year old man presented with cervical lymphadenopathy and weight loss. Lymph node biopsy confirmed fully sensitive *Mycobacterium tuberculosis*. Two weeks after quadruple antituberculosis therapy was commenced he started HAART. His condition worsened with pyrexia, increasing lymphadenopathy, and persistently raised inflammatory markers. Extensive investigation found no other cause. Despite high dose corticosteroids for 8 weeks neither clinical nor biochemical parameters improved. Lymph node suppuration required weekly aspiration that was culture negative after 8 weeks of antibiotic treatment. He continued to deteriorate with weight loss, anaemia, loss of mobility, and further lymph node suppuration. He was started on montelukast 10 mg daily. Two weeks later his general condition had improved and his lymphadenopathy and inflammatory markers had reduced. Other than drainage of a psoas abscess 5 weeks later he improved steadily.

CASE 3

A 22 year old woman presented with fully sensitive pulmonary tuberculosis. She received quadruple anti-tuberculosis therapy but despite complete adherence to therapy her fever continued. Prednisolone 30 mg daily led to a rapid resolution of her symptoms. After 3 months steroids were stopped but 2 weeks later she developed a lymphocytic meningitis with a raised protein of 1.56 g/l. All microbiology (including nucleic acid amplification tests) for bacteria, mycobacteria, fungi and viruses was negative. She improved with prednisolone 40 mg daily that was given for 4 weeks. On stopping the prednisolone her meningitic symptoms returned after 2 weeks. Montelukast 10 mg daily was started and symptoms resolved within a week. Montelukast was stopped after 6 weeks, and symptoms again recurred after 3 weeks. After restarting montelukast her symptoms again resolved. She has continued to take montelukast long term since then.

DISCUSSION

We believe that all three of these cases were caused by an IRD/paradoxical reaction. In all these cases the response to treatment with montelukast was clinically dramatic and in cases 1 and 3 there was relapse and re-control on temporary cessation of montelukast.

One of the possible causes of IRD is a switch from a type 2 to a type 1 cytokine profile.[1 2]

Leukotrienes are increasingly being recognised as key non-specific host derived mediators of antimicrobial defence that may be influenced by inflammatory cytokines,[3] and that

Abbreviations: HAART, highly active anti retroviral therapy; IRD, immune reconstitution disease; LTRA, leukotriene receptor antagonist

Table 1 Patient characteristics

Case	Age	Sex	Ethnic origin	Co-infection	IRD manifestations	Nadir CD4	CD4 at time of montelukast	Zenith VL	VL at time of montelukast	Steroid response	Time to montelucast response
1	36	M	white	Secondary syphilis	Urticarial rash, fever	26	281	>100 000	360	No	24 hours
2	41	M	African	*Mycobacterium tuberculosis*	Increased lymphadenopathy, fever, raised inflammatory markers	18	59	>100 000	<50	No	2 weeks
3	22	F	African	*Mycobacterium tuberculosis*	Lymphocytic meningitis, fever, raised inflammatory markers	620	426	>100 000	>100 000	Yes	1 week

Key messages

- Immune reconstitution can be difficult to manage
- Montelukast, a leukotriene receptor antagonist, appeared to be effective in the cases reported here
- Leukotrienes may be involved in the pathogenesis of immune reconstitution disease

cytokine therapy upregulates decreased neutrophil leukotriene synthesis in HIV infection.[4]

Our findings suggest that IRD may be due, at least in part, to an over-exuberant reconstitution of leukotriene activity. Glucocorticoids have minimal effects on leukotriene synthesis[5] and this may explain the poor response in two of our patients. Montelukast was well tolerated by patients in our case series. Despite the effect we describe there is a theoretical risk of a reduction in montelukast levels after co-administration with CYP3A4 inducers such as rifampicin and antivirals.[6] We conclude that montelukast may have a role in the treatment of HIV related IRD.

CONTRIBUTORS

DW had the original idea to use montelukast; CH and DW reported case 1; EM and EM reported case 2, and RB and ML case 3. All six authors participated in writing the original draft and have seen and approved the final submitted version.

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Conflict of interest: DW has received a grant from Astra Zeneca for a study of zafirlukast (an LTRA) in recurrent vulvovaginal candidiasis

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6 **MSD**. Summary of product characteristics for montelukast.