Toxoplasmosis in immunosuppressed patients

Unanswered questions

*Toxoplasma gondii* has been around a long time. This protozoan parasite, first identified in 1908, is thought to infect up to a third of the world’s population [1]. Cats are the definitive hosts, and humans, along with other warm-blooded animals, are infected by ingestion of food or water contaminated by cat faeces or by consumption of meat containing toxoplasma cysts. The organism can also be transmitted by an organ transplant or blood from an infected donor. An immunocompetent host may experience a self-limiting febrile illness, but in the immunocompromised, the infection can be devastating, with eye or brain involvement or disseminated infection. Infection during pregnancy can result in congenital malformations or miscarriage and *T. gondii* seropositivity has been linked with schizophrenia, bipolar illness and suicidality [2].

There is also increasing evidence that certain strains of toxoplasmosis may cause more severe illness even in immunocompetent hosts [2]. In the USA, toxoplasmosis is the second leading cause of foodborne illness–related death and hospitalization, with >300 deaths and 4000 hospitalizations each year [2]; 4800 people develop visual loss yearly secondary to the parasite [2].

Profound immunosuppression in solid organ or stem cell transplant or advanced HIV disease predisposes patients to toxoplasmosis. However, cases have also been reported in patients undergoing immunosuppressive treatment for inflammatory disorders, including treatment with anti-TNF drugs and other biologic immunosuppressive agents [3]. This is of potential concern given the increase in immunosuppressive drugs for treatment of inflammatory conditions. In the English National Health Service, for example, hospital spending on biologic drugs for the treatment of inflammatory arthropathies, IBD and psoriasis rose from £100 million in 2004 to >£800 million in 2012 [4] (Fig. 1), and the pipeline for further biologics is vast across all areas of medicine.

Although we acknowledge that changes in spending on biologic drugs may be related to changes in cost per dose, we could not find published data describing the use of biologics as number of defined daily doses. Data from the UK General Practice Research Database published in 2012 demonstrated that the proportion of RA patients prescribed DMARDs in the 12 months after diagnosis rose substantially, from 37% to 67% between 1995 and 2010 [5]. This suggests that there are changing treatment paradigms resulting in increased and earlier use of DMARDs in patients with rheumatological illnesses such as RA.

However, basic data on toxoplasma disease are lacking. The US Centers for Disease Control and Prevention has identified toxoplasmosis as one of five neglected parasitic infections for priority action, with aims to address some of the current knowledge gaps and educate health care professionals and the public about toxoplasmosis infection. In the UK, the Advisory Committee on the Microbiological Safety of Food, a subcommittee of the Food Standards Agency, released a report in 2012 entitled Risk profile in relation to toxoplasma in the food chain [6], highlighting the risk of toxoplasma to the immunocompromised patient and identifying the enormous gaps in our knowledge of the condition; but 2 years on, questions about prevalence in livestock, levels of toxoplasma contamination in meat and population prevalence remain unanswered.

A renewed focus on toxoplasmosis in the HIV-negative non-transplant immunocompromised patient is therefore necessary to allow us to fill the gaps of current knowledge. First, data on the prevalence and incidence of toxoplasma infection and disease is absent in HIV-negative immunocompromised hosts. Reporting of adverse events to the regulatory authorities—the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK—is one potential source of data to assess the incidence of toxoplasmosis related to immunosuppressive therapy; however, in the UK, underreporting is clearly a problem. By 1963, 10 cases of toxoplasmosis have been reported to the MHRA as being due to prednisolone, AZA, MMF, tacrolimus and ciclosporin combined [7]; however, we have seen three cases at our institution alone in the past 3 years.

In the absence of robust data from the MHRA, information on the rates of disease can come from a number of sources. Data from randomized control trials of immunosuppressive agents are often not sufficient to draw robust conclusions on rates of opportunistic infection, as the rates of infection are low and follow-up times often short. Meta-analyses can address some of these concerns but are also limited by the follow-up times of the original randomized control trials; large population–based registries provide the best data. Published data are available from a number of the anti-TNF therapies, but not yet for newer agents. Serological evidence of toxoplasmosis is present in 20–70% of the world’s population [1], but risk factors for reactivation and development of disease are poorly understood. Some forms of immunosuppressive therapy may be associated with increased risk of...
reactivation of toxoplasmosis; however, we simply do not have enough evidence to assess the relative risk of the various therapies. High-quality population data on rates of toxoplasma infection in the context of novel immunosuppressive agents are crucial to identify those at risk and to direct prophylaxis, investigation and treatment appropriately.

Secondly, diagnosis of toxoplasma in the immunocompromised is difficult, and questions about the best diagnostic strategy persist. Isolation of *T. gondii* in tissue confirms the diagnosis, but is not sensitive; serology is unreliable in the immunocompromised and PCR is useful but cannot always differentiate between active and latent infection [1].

Thirdly, relatively little is known regarding the efficacy of various treatment regimens with little randomized controlled trial data to guide practice [2]. In addition, published case reports and case series of toxoplasmosis in non-transplant and HIV-negative patients have reported high mortality rates [8]. Finally, the utility of toxoplasma prophylaxis in patients taking immunosuppressive drugs is unclear, with no validated strategy to identify high-risk patients or to guide the choice of prophylactic drug or length of treatment course.

In conclusion, there are significant gaps in many aspects of our knowledge of toxoplasmosis in immunosuppressed non-transplant HIV-negative patients; basic data on the prevalence and incidence of toxoplasma infection and disease are lacking and there are difficulties with diagnostic tests, as well as unanswered questions regarding the best treatment and utility of prophylaxis. For now, it is important for clinicians to maintain a high index of suspicion for this difficult-to-diagnose disease in their immunosuppressed patients and report cases by publishing case reports and via drug registries or national adverse drug reaction reporting systems such as the Yellow Card Reporting System of the MHRA. It is only by doing this that we may begin to answer some of these important questions.

**Funding:** No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

**Disclosure statement:** The authors have declared no conflicts of interest.

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Revised version accepted 11 March 2015

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**References**