

A decade of natalizumab and PML: Has there been a tacit transfer of risk acceptance?

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Abstract

The interplay between each of these stakeholder's responsibilities and desires clearly has resulted in continued widespread use of natalizumab with substantial risks and an ongoing quest for better risk mitigation. In the United States, regulatory actions codified the process of risk acceptance – and risk transfer- by escalating monitoring and information transfer to physicians and patients through Management of medication related risks is a core function of regulatory agencies such as the Food and Drug Administration (FDA), European Medicines Agency (EMA) and the medical community. The interplay between stakeholders in medicine, pharma, regulatory bodies, physicians and patients, sometimes has changed without overt review and discussion. Such is the case for natalizumab, an important and widely used disease modifying therapy for multiple sclerosis. A rather silent but very considerable shift, effectively transferring increased risk for PML to the physicians and patients, has occurred in the past decade. We believe this changed risk should be clearly recognized and considered by all the stakeholders.

History of natalizumab and Multiple Sclerosis

The authors led the first assessment of the risk of natalizumab associated PML as an Independent Adjudication Committee organized to screen research patients exposed to natalizumab. Our assessment found that the risk of PML ranged from 0.2 to 2.8 cases per 1000 exposed persons based on almost 18 months exposure¹. ***During the initial adjudication process, it was understood that the 3 index cases were not the end but the beginning of PML cases associated with natalizumab therapy.***

The authors have closely participated in the subsequent developments from positions in academia, government research and consultation with pharma. Following our assessment, the company received regulatory approval to re-market natalizumab. Natalizumab is now linked to over 645 confirmed PML cases, with a global risk estimate of 3.71 to 4.36 cases per 1000 patients exposed translating to about 1/75 in the highest risk group developing PML². While the 77% survival with PML is much better than observed with PML historically, had the approximately 135 deaths attributed to this complication been clearly articulated at the hearing and the continued accrual of PML cases known, it may well have been more difficult for regulators to approve this therapy. ***While the view in retrospect is clarifying, the view ahead has the benefit of a decade of experience that should be considered by the regulators and others to engage in an ongoing effort to make a valuable therapy for MS safer.***

Natalizumab for other diseases: same drug, different outcomes

The dynamics of therapies moving into practice are influenced by multiple factors. Natalizumab's divergent trajectory for use in MS as compared to inflammatory bowel disease (IBD) illustrates this point. The same medication and risk of PML, when proposed for IBD was deemed unacceptable to European regulators primarily because the modest efficacy did not justify the risks of this drug for IBD.(EMA Doc Ref. EMA/530964/2007) In the US, the FDA deemed the drug approvable in 2008 for moderate to severe Crohn's disease (CD) with similar monitoring to what is used for MS distribution,

effectively shifting the responsibility for risk acceptance to physician and patients. In contrast to the MS scenario, physicians and patients used natalizumab very sparingly in CD, resulting in only three cases of PML in the subsequent decade. This difference is not because IBD patients have a lower risk, but almost surely because so few patients have been exposed. Another parallel example of a biologic with serious risk of PML occurred when cases were associated with prolonged use of efalizumab for psoriasis.^{3,4} While efalizumab's risk estimate for PML is quite similar to natalizumab, efalizumab was voluntarily removed from the market because acceptable alternative therapies were available. (FDA, 4/8/2009) These examples illustrate how similar risks can drive diametrically different regulatory and practice outcomes.

Stakeholders in Medicine

Pharma is established to grow investments in this industry through identification of markets where there is need and avenues to address the medical conditions that will be effective. Their large investments in developing therapies have been essential to generate progress in medicine and support large companies with an emphasis on financial gain. Profit motivation is constrained by regulatory oversight as well as the importance of a strong and positive public image that engenders respect and trust while avoiding behaviors that could threaten unsustainable liability claims. When pharma calculates that a therapy is meritorious, they must prove the efficacy and substantiate the probable risk through large labelling clinical trials to support marketing with an indication through governmental regulatory bodies.

Regulatory agencies are organized to assure that therapies are effective for specific indications, while having an ethically acceptable balance of benefit to risks. When unanticipated toxicities emerge, the regulatory agencies receive harsh criticism and are held accountable. At the same time, these agencies experience constant pressure to speed approval from the medical community seeking new and better

medications as well as pharma wishing to benefit from their investment in drug development . In recent years, the FDA has responded to demands to speed the progress for critical therapies. A good example of this is the acceleration of HIV/AIDS therapies when this epidemic emerged. However, unanticipated risks such as the emergence of PML after marketing approval for natalizumab are reminders to the regulatory agencies that great caution must be applied while introducing novel therapy.

Physicians are gatekeepers for prescribed drugs. They are trained to diagnose diseases and weigh evidence for efficacy and toxicity of possible treatments in light of the patient's overall status when prescribing optimal therapy. While holding the virtue of unfailing defense of their patient's wellbeing, and hired by the patient to recommend wisely, physicians are challenged by lack of time, competing sources of information and pressures to offer cost effective strategies for their practice as well as their patients. Complex discussions of risk may take much time and effort, and can even dissuade patients from therapies that many would consider optimal.

Meanwhile, patients and their families deserve and expect to make the final choices of how they are to confront their medical conditions. However, it is challenging to equip typical patients with enough information to allow them to ethically assume responsibility for difficult medical decisions. Conflicting opinions, typical in any complex issue, are confusing and stressful for patients who often default to their doctor's recommendation while not fully considering the consequences of risks they are assuming. Much misinformation is commonly available and very often salient parts of information short circuit needed full consideration of options and risks. At the same time, the impact of living with difficult conditions such as MS or IBD are powerful motivators to assume significant risks.

the TOUCH (Tysabri Outreach Unified Commitment to Health[®], Biogen) program. This program limits prescribers to those with significant experience and training appropriate to prescribing a riskier medication, and requires monthly queries of patients seeking symptoms and reconfirming at least the

acceptance of the potential complication of PML. Critically, the European experience where a standard risk mitigation program was not instituted, has resulted in no worse, and potentially superior outcomes with regard to PML incidence and survival.⁵ Thus, the merits of risk mitigation through programs such as TOUCH deserve scrutiny before they are adapted to other challenges in health care⁶. We view this process as a formalized, tacit passing of responsibility of risk acceptance from regulatory to end users of therapy as an unproven approach. This has evolved over time in attempts to mitigate PML risk, while assuring that all parties remain informed.

This outcome was not a foregone conclusion given these risks and drugs. In the case of efalizumab, pharma and regulators agreed to remove the drug, effectively taking responsibility to protect patients from this risk. In the case of natalizumab for IBD, in Europe regulatory agencies again took the choice away for individuals by not approving the drug for IBD, while in the US FDA regulations appear to transfer decision about this risk through physicians to patients. Since the FDA decision supporting marketing natalizumab for MS, recognized PML risks have at least tripled, and in higher risk populations are an order of magnitude greater than originally estimated. Further, there have been multiple new therapies approved for multiple sclerosis.

The history of natalizumab therapy emphasizes the variable roles that have been assumed by stakeholders in the management of benefits and risks. It demonstrates how risk acceptance has been transferred from the industry and regulators to the physicians and patients. In many ways this system has worked extremely well, maintaining the availability of a sorely needed drug, while stimulating development of increasingly sophisticated risk prediction and potentially mitigation strategies. Risks have not been denied and indeed increasing risks have been clearly communicated through a regularly updated physician website. (Biogen) Parties maintaining that patients should have the opportunity to make decisions including those where they assume substantial risks in hopes of unique benefits will be

satisfied. Others who want our regulatory systems to shield patients from very significant risks that may exceed the special benefits could wish for more stringent controls for such drugs. Regardless, ongoing commitment by professionals to understand and communicate the nuanced and difficult decision of how to weigh benefit and risk so that patients can make the right choice is critical. Our healthcare system must therefore support physician's time invested in this critical part of health care, and the importance of controlling the conflicts of interest that might influence physician's recommendation in any way that is not focused on seeking the best outcome for patients and therefore for society. Perhaps the best pathway forward would be to better mitigate the PML risk for the patients by finding better tools to define exactly those patients at greatest risk⁷. The plan that is currently in use is a good start but with 8-10 new PML cases arising per month over the last decade, additional parameters should be explored. That is another challenge that should not need another decade to resolve.

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While the view from the rear view mirror is clarifying, the view ahead has the clarity of a decade of experience that should be considered by the regulators and others to engage in a new discussion.

Making a valuable therapy for MS safer should be the goal achieved by all the stakeholders.

During the initial adjudication process, it became clear in discussions that the 3 index cases were not the end but the beginning of PML cases associated with natalizumab therapy.