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A proposed bailout for A-T patients?

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These are times of economic crises and proposed bailouts of failing systems. A proposal has recently been put forward for treating patients with ataxia-telangiectasia (A-T): Betamethasone partially restores neurological functions [1–3]. The questions being asked are very similar: Will it work? For how long? What are the potential dangers and costs? Most interestingly, there seem to be some *unexpected* lessons to be learned from clinical trials – and, thus, the metaphor may aptly apply back upon the economic sector as to which remedies work and which do not.

Ataxia-telangiectasia is an autosomal recessive cerebellar ataxia with onset between 1–4 years of age [4–7]. A-T arises from mutations in the ataxia-telangiectasia mutated (ATM) gene which encodes a ubiquitous serine-threonine kinase. The incidence of A-T is approximately one in 100 000 live births; however, this varies with the coefficient of inbreeding within an ethnic group. The most common presenting complaints are unsteadiness of gast and slurred speech. Apraxia of eye movements is almost always present as well. Cancer (e.g. leukemia, lymphoma, and others) affects roughly one-third of patients and is occasionally the presenting complaint. This creates a dangerous situation when radiation therapy is recommended without the realization that these patients are also radiosensitive and conventional doses of radiation are contraindicated and often lethal. A clinical diagnosis can be confirmed by elevated serum alphafetoprotein, an undetectable ATM protein on western blotting, and radiosensitivity testing [8]. A new rapid assay for diagnosis, which also promises to identify carriers, has recently been described [9]. No effective disease-modifying therapy is presently available, although supportive therapy includes medications that control drooling and tremors. Aggressive physical therapy prevents contractures and minimizes lung infections Speech therapy improves enunciation and, thereby, schoolwork and social relationships.

The potential benefits of glucocorticoids for A-T have been considered before. A-T patients often develop lymphoid malignancies, for which treatment regimens usually include glucocorticoids or ‘steroids’. Parents of patients receiving glucocorticoids have been quick to point out that the neurological symptoms diminish, sometimes dramatically, during treatment. This led to attempts in the 1980s to focus on the use of these drugs for long-term treatment of the neurological problems [10]. Whilst it was clear that they *did* reduce symptoms, it seemed equally clear that once discontinued, the symptoms reappeared. This has also been the recent experience of Buoni *et al.* [1], who described a 3-year-old boy with both A-T and bronchial asthma in whom the ataxia improved whenever the asthma was being treated with betamethasone (the accompanying videos were both impressive and encouraging). Broccoletti *et al.* [2] followed up by administering betamethasone (0.1 mg/kg/

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day) for 10 days to six consecutive patients ranging in age from 5–30 years. All but one improved, with the most striking improvement being observed in speech, stance and finger-chase items. Notably, the greatest clinical improvements were seen in the two younger patients, in whom MRI changes were not yet present. One patient maintained slight improvement for a week after steroids was discontinued.

The issue then becomes one of benefit-to-risk. These patients gain weight and become 'Cushingoid' from the steroids just as any other patient would. They are already immunocompromised by the underlying absence of ATM protein. Roughly two-thirds of A-T patients manifest both humoral and cellular immune deficiencies, including lymphopenia, reduced T and B cell responses, IgA and IgG2 deficiency, and poor antibody responses to lipopolysaccharide antigens, such as pneumococcal vaccines [11–16]. Whilst the immunodeficiency has often been suggested as the cause of the increased cancer susceptibility, recent data suggest that the cancers most probably result from inefficient recognition and repair of double strand DNA breaks, leading to larger chromosomal aberrations and the development of malignant clones [17–22].

Glucocorticoids are known to reduce both inflammatory and immune responses, which can increase the frequency of infections. Furthermore, bones weaken and fracture, especially in inactive patients, and growth is retarded. Thus, long-term steroid use in such patients would initially appear to be a step in the wrong direction, especially when one considers that all but the most severely affected A-T patients continue to function fairly well at home and in school until about age 8. Also, at age 8, it is still extremely difficult to predict the long-term outcome of the natural disease.

This is not to say that anti-inflammatory agents might not have a role in slowing the progressive neurodegeneration. ATM kinase, the missing protein in A-T, is thought to phosphorylate over 700 downstream substrates [23] and these proteins impact on many pathways and provide many potential targets upon which steroids might act. Apoptosis is deficient; p53 is not activated efficiently by ATM nor protected from degradation [18,22,24–27]. NFκB, another transcription factor with myriad targets, is also phosphorylated by ATM kinase [28]. Both the Fois [1] and Pignata [2] groups have considered substituting other glucocorticoids that might be less toxic or perhaps cross the blood–brain barrier more efficiently. Methylprednisolone had no beneficial effect. Perhaps some of the newer anti-inflammatory agents in development may prove more suitable for long-term use in A-T patients [29].

Alternatively, could the effects of betamethasone result from its activity as an antioxidant? A-T cells react poorly to oxidative stress [30]. As well, oxidative stress plays a major role in neural degeneration [31,32]. The possible antioxidant mechanism is addressed by Russo *et al.* [3] in this issue. In a very limited study, the authors measured intracellular glutathione levels, reactive oxygen species (ROS) production, and lipid peroxidation in the same six A-T patients receiving betamethasone for 10 days [2]. They compared some of these results to clinical improvement, as assessed by SARA – a clinical Scale for the Assessment and Rating of Ataxia. A marked reduction in ROS levels was observed in one patient, suggesting that antioxidative mechanisms may play a role in improving the cerebellar function. However, once again, in their final figure, we see that ROS levels had returned to normal only 7 days after discontinuing the betamethasone.

The study further suggests that ROS levels might serve as a biomarker for predicting which patients might be the best candidates for betamethasone treatment. Other biomarkers to consider might be: (i) the levels of ATM kinase activity in peripheral blood lymphocytes of patients, (ii) using a kinetic response curve for the phosphorylation of SMC1 after cells have

been damaged by bleomycin or irradiation [9], or 3) certain ATM mutations may render some A-T patients more responsive to steroid treatment. It is interesting that despite clinical improvement with betamethasone, the elevated serum alphafetoprotein did not change in the single patient in whom such measurements were reported [1].

As with other clinical trials for chronic diseases, it will be very difficult to select whether to use subjects who are older and more severely affected, or younger less affected children. What is most interesting about the present studies is that symptomatic neurological improvement was observed within 1 week of starting betamethasone, despite 3–21 years of previous neurological deterioration! This rapid turnabout argues strongly against the need for cellular replacements and the reestablishment of neural synapses and circuitry, which usually take months or years. The rapid reversibility also provides strong encouragement for the development of other therapeutic approaches, such as antioxidants and mutation-targeted therapy [33–36]. On the other hand, the observation that older patients did not respond as well as younger ones suggests that a threshold level of Purkinje cell numbers or other cerebellar hard-wiring may be a prerequisite for successful steroid therapy in A-T [37].

Thus, on the basis of very limited studies, it would appear that steroids must remain within the armamentarium of *supportive* medicine for A-T until further evidence can be gathered as to their potential role as *disease-modifying* agents. The bailout at this juncture seems to be only a temporary holding action and the lurking costs and risks are still difficult to assess. Unraveling the molecular pathogenesis of A-T remains the most promising road to a disease-modifying treatment.

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