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EDITORIAL

A rational pharmacologic approach toward a biologically meaningful subtype of autism spectrum disorder☆,☆☆

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Social communication and social interaction deficits are core symptoms of autism spectrum disorder (ASD), a clinically and etiologically heterogeneous neurodevelopmental condition. The heterogeneity of ASD has led to significant challenges in developing effective interventions for its core symptoms, suggesting a need to define and utilize clinical subtypes of ASD to guide the discovery of novel treatments. An immune-mediated subtype of ASD, characterized by systemic, multi-organ inflammation or immune dysregulation, is one such subtype which has been postulated by multiple groups and may serve as a guide to discovering novel interventions.[1–4] The randomized clinical trial assessing the efficacy of prednisolone, a synthetic immunosuppressive, on language function in children with ASD reported by Brito et al. in this issue of the *Jornal de Pediatria* represents a very important step in this direction.[5]

As the evidence base for immune dysregulation in a subset of patients with ASD grows, there has been increased interest in the role of immunomodulation for the treatment of core symptoms. In fact, the only two treatments for ASD currently indicated by the Food and Drug Administration (FDA), risperidone and aripiprazole – both second-generation antipsychotics approved for the treatment of severe irritability in children and adolescents with ASD – have demonstrated anti-inflammatory effects in cell culture and animal model studies.[6–8] Additionally, more than ten medications known to have immunomodulatory potential have been repurposed from other fields of medicine to undergo pilot investigations in either animal or initial human studies to determine whether they may modify the core symptoms of ASD (reviewed here).[9] For example, pioglitazone, an anti-diabetic medication which is known to exert anti-inflammatory activity on astroglial cells of the brain,[10] has been demonstrated to improve social interactions and normalize ultrasonic vocalizations in a rat model of maternal immune activation-mediated ASD through decreasing interleukin-6, an inflammatory cytokine.[11] A follow-up open-label study demonstrated that children who received daily treatment with pioglitazone for three to four months had improvements in four out of five subscales of the Aberrant Behavior Checklist: irritability, lethargy, stereotypy, and hyperactivity.[12] Some other medications that have shown initial promise and merit further investigation for treating the core symptoms of ASD through immunomodulation include minocycline, valproic acid, and celecoxib.

Although immunomodulatory treatments for ASD represent an exciting, potentially new avenue for drug discovery, they are not currently the standard of care for ASD and much more research needs to be done to establish safety, tolerability, and efficacy. There are several factors to consider

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when conducting these studies. First, it will be important to identify the neurodevelopmental time points that are most sensitive to treatment with an immunomodulatory agent. Since acquisition of social and communication skills typically occurs during specific developmental periods, there may be timeframes before or during which immunomodulatory treatments are most impactful. The observation that there was an interaction between age and prednisolone administration, such that the younger group of children (<5 years) had a more robust response to prednisolone in the study by Brito et al.,[5] lends credence to this hypothesis. Second, there is still no evidence to assist in the identification of the subset of patients with ASD who may be more likely to respond to immunomodulatory treatments. Further studies on how to utilize a clinical phenotype and/or inflammatory biomarkers to identify this subset of patients and monitor the physiological response to treatment will be of great value. The fact that all of the participants in the study by Brito et al.[5] underwent brain magnetic resonance imaging (MRI) and lumbar punctures is a remarkable feat, as participation in neuroimaging studies can be very difficult for adults, let alone children with ASD.[13] It would be of interest to know if any of the MRI or cerebrospinal fluid findings correlated with response to prednisolone and could be used as biomarkers to predict response to immunomodulatory treatments. Perhaps the authors plan to report these findings in subsequent manuscripts. Since the inclusion criteria for the randomized clinical trial in the study by Brito et al.[5] were not explicitly limited to children with a pro-inflammatory profile (such as co-occurring inflammatory medical conditions or a family history of autoimmunity), this may have attenuated the observed effect of prednisolone on language improvement. The observation that there was an interaction between developmental regression and prednisolone suggests this phenomenon may be a marker of an inflammatory-subtype of ASD and this should be further investigated. Finally, future studies will need to determine whether there are sex-specific responses to immunomodulatory treatments. Preclinical studies have demonstrated that in mouse maternal immune activation models of ASD, offspring exhibit sex-specific changes in gene expression affecting hundreds of genes.[14] Furthermore, a two-hit (prenatal and early postnatal) mouse model of early-life immune activation demonstrated that male offspring exhibit a more severe ASD phenotype than female offspring.[15] In this model, both sexes exhibited increased pro-inflammatory gene expression in the brain, but only males exhibited decreased expression of anti-inflammatory genes.[15] The study by Brito et al. understandably only included boys to reduce sample heterogeneity. However, these recent preclinical findings suggest that it may be important to include girls in future studies to determine whether there is a sex-specific response to immunomodulatory treatments.

There are many challenges to designing and conducting clinical trials in ASD. As in any drug study, patient recruitment is the first major challenge. However, recruiting an adequate number of patients to demonstrate a treatment effect of a medication for ASD is magnified by the fact that ASD is a heterogeneous and behaviorally-defined disorder. There are no well-established biomarkers that can be used to diagnose or characterize patients with ASD. Because of this, there is a need to recruit a larger sample size to attain adequate power. Highlighting the practical challenges of recruiting and enrolling children with ASD in a medication study, the study by Brito et al. was registered ten years ago in 2010 and screened more than 100 children to enroll 40 research subjects.[5]

The second challenge in clinical trial design for subjects with ASD is the decision regarding which primary and secondary outcome scales to include, balancing the need to use well-recognized measures in the field with scales that are culturally appropriate and validated for the subjects included in the trial. Brito et al. navigated this challenge by utilizing an internationally recognized scale, as well as two Brazilian instruments. The authors used a clinical rating scale of autism, the Childhood Autism Rating Scale (CARS-BR),[16] to assess secondary outcomes. Although the results of the CARS-BR do not appear to be included in this report, it would be of interest to know if treatment with prednisolone resulted in any changes in the CARS-BR. The authors chose to assess language using two Brazilian instruments: the Child Language Test in Phonology, Vocabulary, Fluency, and Pragmatics (ABFW), a test of pragmatic language, and the Language Development Assessment (ADL) based on the Preschool Language Scale.[17]

Third, there are significant challenges to interpreting the results of a clinical trial of small sample size. The study by Brito et al. included 18 children who were randomized to prednisolone treatment and 20 children who were randomized to placebo.[5] The results demonstrated no significant effect of prednisolone on either the ADL global language scores or the ABFW total communicative acts. However, there were some statistically significant interactions between prednisolone and age; prednisolone and history of regression; as well as prednisolone, age, and regression history in some of the ABFW subscales. These interactions suggest that prednisolone may have a greater effect on language development in younger children and in those with a history of developmental regression, and possibly an even larger effect in patients with both these clinical characteristics. While the sample size was limited (only 13 of the 18 subjects randomized to prednisolone were under 5 years of age) and the study was not adequately powered to draw these conclusions with confidence, the authors of the study were aware of these limitations. They note that randomization which accounts for the presence or absence of developmental regression would allow for a more equitable distribution of subgroups for comparison. This randomization approach may be helpful to include in future studies. The statistically significant interactions observed between prednisolone administration and age – as well as a history of developmental regression – are very interesting and deserve further study with a larger sample size. In summary, there are no statistically significant findings overall, likely due to small sample size and a heterogeneous population, but there are intriguing hints that there may be a clinically identifiable subgroup of children with ASD who respond to immunomodulation. Notably, this study contributes important published data on the relative tolerability and safety of prednisolone in children with ASD for others to build upon. While the primary outcomes of the study were negative, the authors should be commended for publishing the results of this important and pioneering work, as these results provide initial evidence

supporting the need for future work on immunomodulatory treatments in ASD.

Based on what we have learned from this trial, future studies on immunomodulatory treatments in ASD will need to be designed and adequately powered to confirm whether certain clinical features including a history of developmental regression and younger age predict response to immunomodulatory treatments. Although many immunomodulatory treatments are associated with significant side effects that carry the risk of unblinding, the authors in this study made considerable efforts to protect the blind by ensuring that the language scale raters were not part of the participants' clinical care team and were unaware of randomization allocation. Pre- and post-treatment language assessments using internationally recognized and well-validated scales should be included in future work. Finally, future studies might benefit from including additional baseline demographic descriptors including validated cognitive and adaptive functioning measures, family history of inflammatory conditions, the presence of medical and psychiatric co-morbidities, and include inflammatory biomarkers to advance our ability to identify patients who may be most responsive to immunomodulatory treatments.

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Conflicts of interest

The authors declare no conflicts of interest.

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