VIEWPOINT

Paving the Way Toward Meaningful Trials in Ataxias: An Ataxia Global Initiative Perspective

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Ataxias, in particular if of genetic origin, have long been considered untreatable. They are now becoming models for the development of targeted molecular therapies due to their defined genetic etiology. The current decade will thus translate the advance in genomics of ataxias, which has allowed the unraveling of almost 50 autosomal dominant spinocerebellar ataxias (SCAs) and more than 100 autosomal recessive ataxia (ARCA) genes, into therapy approaches based on the underlying gene mutations and derived molecular mechanisms.[1-3] The most advanced of them will now cross the threshold to clinical trials, raising hopes for availability of effective molecular treatments for specific ataxias within the next years. To facilitate the clinical development of therapies for ataxias, a worldwide research platform, the Ataxia Global Initiative (AGI), was recently established.

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Members of the AGI consortium are listed in the Appendix.

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Genetic Ataxias: Forerunners for Targeted Therapy Development

Although small molecules had been the mainstay of drug therapy since the beginning of modern medicine, biomedical research has recently developed an arsenal of macromolecules that complement the small-molecule approach and may be particularly suitable for the treatment of genetic diseases. These options are further expanded by gene-based therapies.[4]

Currently, antisense oligonucleotides (ASOs) inducing cleavage of the RNA encoding the presumably toxic disease proteins are a main focus of therapy development for ataxias. Such ASOs already underwent successful early-phase clinical trials in Huntington's disease and superoxide dismutase 1 amyotrophic lateral sclerosis (SOD1 ALS).[5,6] However, subsequent phase 3 trials did not prove clinical efficacy, but a positive effect on fluid biomarkers in SOD1 ALS (https://investors.biogen.com/news-releases/news-release-details/biogen-announces-topline-results-tofersen-phase-3-study-and-its). In animal models of SCAs caused by CAG repeat expansions, such ASOs proved to be effective, and phase 1/2 trials in polyglutamine SCAs are imminent (ClinicalTrials.gov: NCT05160558).[7,8] ASOs that modulate splicing promise even wider applications, including individualized treatments in single patients.[9] Such interventions are currently being developed for ataxia telangiectasia and optic atrophy 1, a disease often associated with ataxia.[9,10] Another line of development is adeno-associated virus-based gene therapies to deliver small interfering RNAs or microRNAs targeting genes coding for toxic proteins.[11]

Efficient delivery still presents a major bottleneck for the clinical application of ASOs and viral vectors. Distribution of ASOs in the brain after intrathecal injection appears sufficient for several ASO types, but the repeated injections are a burden for patients.[12] Gene therapy with viral vectors has the advantage of a single-dose application. However, many questions regarding vector design, immunogenicity, route of application, and distribution are still awaiting final anwers.[13]

Joint Action of all Stakeholders as the Key to Success: The Ataxia Global Initiative

Although manifold promising new treatment approaches for ataxias are on the way, a number of major challenges stand in the way of successful trials. These include: (1) limited access to existing clinical data, (2) inappropriate sensitivity and questionable patient relevance of outcome assessments, (3) lack of validated biomarkers, and (4) absence of an effective trial infrastructure. To address these challenges in a timely and effective manner and facilitate the clinical development of therapies for ataxias, we established the AGI in 2021 (https://ataxia-global-initiative.net/). The AGI is a worldwide research platform formed by individual members, including academic or industry-based ataxia researchers, clinical investigators, ataxia clinicians, and representatives of patient organizations. Currently, AGI has 185 members from 29 countries. In addition, the AGI is partnering with industry companies and patient organizations (Fig. 1).

To achieve its goals, the AGI has established an organizational structure consisting of multistakeholder working groups and trial-readiness services, including the AGI Trial Site Registry and the Ataxia Advisory Committee Therapy.[14] The AGI Trial Site Registry provides information on personnel, facilities, and ataxia patient populations at the participating sites around the globe in a readily available, standardized fashion. The Ataxia Advisory Committee Therapy allows academic groups and companies to have their preclinical and clinical development plans evaluated by an international board of preclinical, clinical, regulatory, and industrial experts, as well as patient representatives, with the aim to de-risk therapy development (Fig. 2). In addition, the AGI started a collaboration with the Critical Path Institute resulting in the launch of the Critical Path to Therapeutics for the Ataxias (CPTA), which has a specific focus on data sharing and driving toward regulatory acceptance of clinical and biomarker outcomes for clinical trials (https://c-path.org/programs/cpta/).

AGI is sharing information and resources via the AGI website (https://ataxia-global-initiative.net), a monthly AGI newsletter (received by more than 700 people), and scientific conferences and symposia specifically focused on therapy development and trial readiness. To foster ataxia expertise of young clinicians, the AGI Young Investigator Initiative has started to implement an AGI training curriculum including a regular webinar on various methods of ataxia outcome measures, open to participation for all people interested in ataxia research. To provide information about ataxia research to laypeople, patient organizations can play an important role, and there is representation both in the Steering Committee and in the membership of AGI. In addition, AGI has started a partnership with SCASource (https://scasource.net/), which is an online multilingual platform that disseminates ataxia research news in lay language.[15]

Availability and Aggregation of Natural History Data for Robust Trial Design

Reliable natural history data are key for trial design. Although longitudinal cohort data are available for the

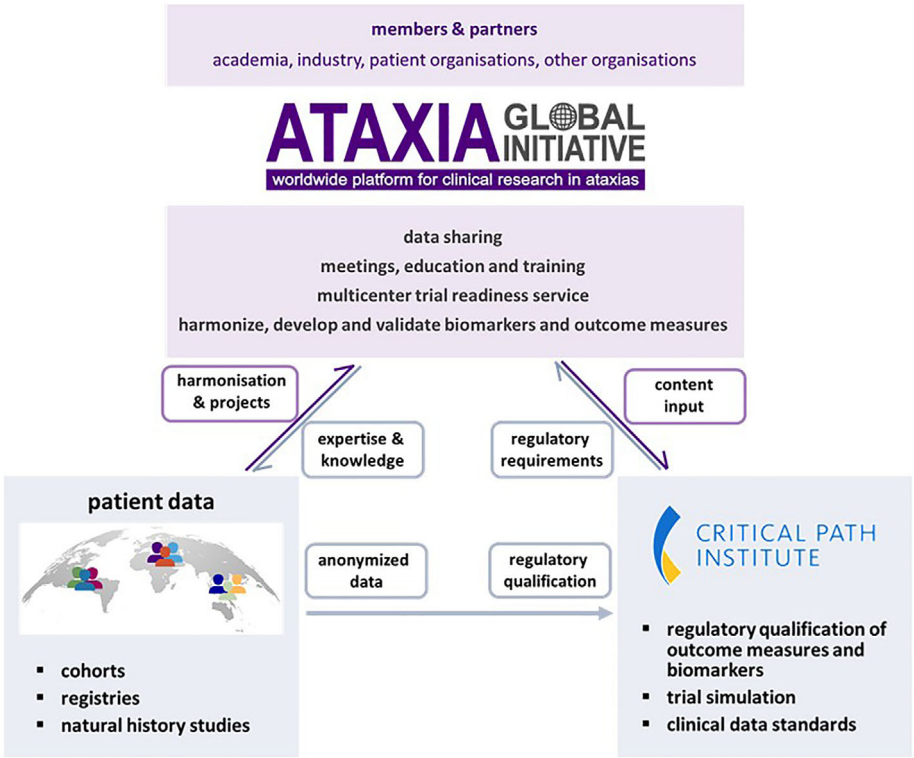

FIG. 1. Organizational structure of the Ataxia Global Initiative (AGI).

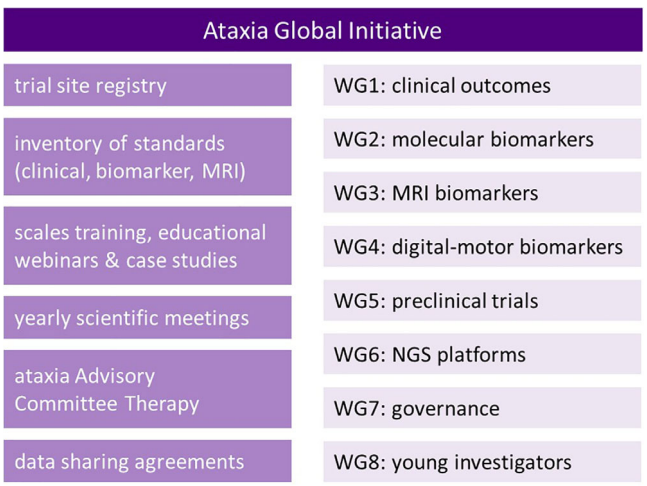

FIG. 2. Resources and working groups of the Ataxia Global Initiative (AGI). MRI, magnetic resonance imaging; NGS, next generation sequencing.

main CAG repeat SCAs (SCA1, SCA2, SCA3, and SCA6) and the most frequent ARCAs (Friedreich ataxia, ARSACS, SPG7, and RFC1 disease),[16-19] they are missing for the large majority of other SCAs and ARCAs. Extensive efforts are thus undertaken by AGI partners to map the natural history of other SCAs and ARCAs. The AGI is in an ideal position to serve as a platform for sharing and exchanging these data. To facilitate this, the AGI is developing procedures and preparing templates that help to overcome the related legal and administrative hurdles. One ongoing initiative to bring together existing natural history data of genetic ataxias is coordinated by the CPTA.

However, novel, more in-depth and rigorous natural history studies are needed to provide more robust trial-like natural history and biomarker data. Although the first such natural history studies are currently undertaken by AGI partners (Biomarkers and Genetic Modifierers in Pre and Postsymptomatic SCA3/MJD, BIGPRO, The Clinical Research Consortium for the Study of Ataxia, CRC-SCA, European Spinocerebellar Ataxia type 3/Machado Joseph Disease Initiative, ESMI, Integrated Multimodal Progression Chart in Spastic Ataxias, PROSPAX, Clinical Trial Readiness for SCA1 and SCA3, READISCA, and others), more dedicated public and industry funding for such studies is needed, with the AGI ideally positioned to coordinate such multicenter endeavors on a global scale.

Cross-Center Standardized Outcome Assessment for All Main Outcome Domains

Both planning and execution of trials is challenged by large between- and even within-center variability in outcome assessment. This includes literally all outcome domains, for example, variability in clinical, digital,

imaging, and molecular outcome assessment. To overcome this challenge, the AGI has established cross-center harmonized standard operating procedures for each major outcome domain, including clinical, fluid biomarker, magnetic resonance (MR) imaging, and digital-motor assessments, complemented by standardized training tools, such as the Scale for the Assessment and Rating of Ataxia (SARA) training tool (https://ataxia-global-initiative.net/resources/sara-training-tool/), and recorded training webinars.

Clinical Outcome Parameters: Sensitivity to Change and Patient Meaningfulness

Given the relatively slow progression of most SCAs and ARCAs with survival times exceeding 20 years after ataxia onset,[20] clinical outcome parameters for trials need to be sufficiently sensitive to change. Although SARA serves as the most widely applied primary clinical outcome for genetic ataxias, there is substantial intraindividual variability, reaching almost 20% of the entire scale range on repeated testing within 14 days.[21] Thus, various sample size calculations come to the unanimous conclusion that, in a trial of at least 1 year in duration, several hundreds of participants would be needed to detect a disease-slowing effect of an investigational drug.[16,22] There is an ongoing debate whether modified SARA versions, such as the Modified Functional SARA that is used in an ongoing drug trial (https://clinicaltrials.gov/ct2/show/NCT03701399), have higher sensitivity. A thorough analysis of properties of SARA, potential modification of the scale, and careful analysis and validation of possible new versions are some of the main tasks of the AGI together with CPTA.

Nevertheless, there is an obvious need to follow new strategies to improve clinical assessment that go beyond application of clinical scales in the hospital. One approach developed by AGI partners is ataxia capture by body-worn sensors.[23-25] Further improvement can be achieved by shifting the assessment into real life, either by repeated video capture ($SARA^{home}$) or body-worn sensors, which has shown to dramatically reduce calculated sample sizes.[21,25,26]

Standard clinical ataxia scales such as the SARA need to show that they capture not just neurological proxies of ataxia functions, but indeed reflect meaningful benefit of patients' lives. This challenge might be alleviated by correlating change in SARA with change in patient-reported outcomes reflecting patients' daily life impact more closely, for example, the Friedreich Ataxia Rating Scale Activity of Daily Living scale,[27] the PROM-Ataxia,[28] and other patient-reported outcomes currently under development by AGI partners, leveraging the worldwide AGI infrastructure and its close interaction with patient organization, such as the National Ataxia Foundation or Ataxia UK. AGI partners are currently about to start a project on the worldwide evaluation of Patient Reported Outcome Measure of Ataxia (PROM-Ataxia) and Friedreich Ataxia Rating Scale Activity of Daily Living with the goal to make them available in more languages, to assess them longitudinally in a multicenter setting, and to directly compare them. An alternative innovative novel approach to overcome this challenge might be to establish a patient-ranked order of function of the respective disease functions and disease scale domains, as developed for ALS.[29]

Development of Validated Biomarkers

For early-phase clinical trials, there is an urgent need for biomarkers that are sensitive to detect treatment efficacy in small groups of patients before moving to large and registration trials with primary clinical outcomes. Currently, blood concentrations of neurofilament light chain, a marker of axonal injury,[30,31] gait-related sensor data,[25] and a number of MR imaging measures, including regional brain volumes,[32,33] diffusion tensor imaging-derived measures,[34] and neurochemical abnormalities detected by MR spectroscopy,[35] are the most promising biomarker candidates.

In the future, preventive trials in preataxic mutation carriers will also be a realistic option. In such trials, the number of patients converted to manifest disease could serve as a primary outcome, as in the recently started ATLAS (Adults With a Confirmed Superoxide Dismutase 1 Mutation) trial for ALS (https://clinicaltrials.gov/ct2/show/NCT04856982). This approach, however, requires a trial population that is enriched for proximity to conversion to manifest disease. This can be achieved by stratifying preataxic patients based on genetic information and biomarker results, because all biomarkers mentioned earlier showed increasing abnormalities with proximity to ataxia onset. The same biomarkers may also be considered as primary outcomes in trials with premanifest disease.

Trial Infrastructure and Availability of Trial-Ready Patients

The presence of an appropriate infrastructure for clinical trials with access to well-characterized, genetically stratified patients is the prerequisite for trial readiness in genetic ataxias. The existing consortia that are running natural history studies provide valuable data. However, more can be done to assist trial readiness

globally. To this end, the AGI Trial Site Registry is being established that provides reliable information on the local infrastructures available in centers worldwide for ataxia trials and on precise numbers of trial-ready patients.

Results from recent trials in neurodegenerative diseases, specifically the NURTURE study in infants with spinal muscular atrophy, suggest superior efficacy of targeted treatments initiated in premanifest or early disease stages compared with those initiated later.[36] This fact highlights the challenge to develop strategies to efficiently identify and recruit ataxia subjects in early or even preataxic disease stages. For autosomal dominant ataxias, this seems possible via research programs that systematically focus on family-based recruitment of preataxic relatives of symptomatic index patients.[37-39] Such programs must be combined with adequate support and counseling.

It seems more difficult in practice, however, for all ARCAs. Due to the autosomal recessive inheritance, patients usually come to medical attendance only when first symptoms have developed and are often already in mild to moderate disease stage on first visit to trial referral sites. These observations highlight the need for specific screening programs to identify so far genetically undiagnosed patients who belong to the group of potentially treatable ARCAs, for example, by systematic genetic, phenotype, machine learning–, or biomarker-based screening approaches. Successful exemplary approaches in each of these domains have already been developed, for example, for Niemann-Pick Type C ataxia,[40] and will now be further advanced by the AGI. ■

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Appendix

Members of the AGI consortium, including working group leads and office, are as follows: Sirio Cocozza (Department of Advanced Biomedical Sciences, University of Naples "Federico II", Naples, Italy); Jennifer Faber (German Center for Neurodegenerative Diseases [DZNE], Bonn, Germany; Department of Neurology, University Hospital Bonn, Bonn, Germany); Brent Fogel (Departments of Human Genetics and Neurology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; Ian Harding (Department of Neuroscience, Central Clinical School, Monash University, Melbourne, Australia; Monash Biomedical Imaging, Monash University, Melbourne, Australia); Pierre-Gilles Henry (Center for Magnetic Resonance Research, University of Minnesota, MN, USA); Heike Jacobi (Department of Neurology, University Hospital Heidelberg, Heidelberg, Germany); Francesca Maltecca (Neurogenomics Unit, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milan, Italy); David Mengel (Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany); Andrea Nemeth (Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom; Oxford Centre for Genomic Medicine, Oxford University Hospitals NHS Trust, Oxford, United Kingdom); Puneet Opal (Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA); Gulin Oz (Center for Magnetic Resonance Research, University of Minnesota, MN, USA); Hélène Puccio (Institut Neuromyogène, Inserm, Lyon, France); Filippo Santorelli (Molecular Medicine, IRCCS Fondazione Stella Maris, Pisa, Italy); Andreas Traschütz (Division Translational Genomics of Neurodegenerative Diseases, Center for Neurology and Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany); Adam Vogel (Centre for Neuroscience of Speech, The University of Melbourne, Victoria, Australia); Stephan Zuchner (Dr. John T. Macdonald Foundation Department of Human Genetics and John P. Hussman Institute for Human Genomics, University of Miami, Miller School of Medicine, Miami, FL, USA); Annemarie Post (Institute for Medical Genetic and Applied Genomics, Centre for Rare Diseases, University Hospital Tübingen, Tübingen, Germany); and Birte Zurek (Institute for Medical Genetic and Applied Genomics, Centre for Rare Diseases, University Hospital Tübingen, Tübingen, Germany). ■

Data Availability Statement

This is a viewpoint paper that does not report data.

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