BC-007: Will the „German miracle“ also work for ME/CFS ?

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Abstract

The aptamere BC-007 has shown preliminary promise as a potential pharmaceutical therapy against Long Covid and is currently under investigation in a clinical study. Several questions remain to be answered, among them: How does BC-007 work? How can the apparent remission of several months duration after a one time infusion be explained? And: Can the drug also be effective against Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)?

BC-007 (aka ARC183) is a single-stranded DNA oligonucleotide aptamere originally developed as a thrombin inhibitor in the US and then re-purposed as a broad spectrum neutralizer of G-Protein Coupled Receptor (GPCR) auto-antibodies in cardiomyopathy by a research team around Gerd Wallukat (then at the Max-Delbrück-Centrum for molecular medicine in Berlin/Germany), now working at the German biotech start-up Berlin Cures.[1], [2]

BC-007 binds to several GPCR auto-antibodies (aabs), to certain antigens (including SARS-CoV-2 antigens) and possibly to other, as of yet undefined, antibodies and/or antigens. Experimental therapy with BC-007 has shown surprisingly positive therapeutic results in a severely affected Long Covid (LC) patient, who has apparently been back to gainful employment and full activity for about 3 months after a one-time infusion therapy.[3] The potential efficacy of BC-007 – which has been reported to be cheap in production as well as well tolerated - has since been confirmed in at least two other LC patients.[4] A controlled clinical trial on LC patients is being planned and will start in 2022 after full approval. One of the investigators has stated that they are planning to also do a trial with the drug on ME/CFS patients (here, a timeline has not been offered so far). For details on BC-007, see [3].

It may be of note that other therapies that may possibly work through the removal of aabs have been explored in ME/CFS. A trial of immunoadsorption has reported positive results in some (but not all) patients.[5], [6] Also ME/CFS cases treated with INUSpheresis have been reported, with clinical improvement of the patients treated and an apparent reduction of 50% of the GPCR aab levels measured.[7] Also, a trial using HELP-aphareses (which may or may not also affect aab levels) has been done in Long Covid and ME/CFS patients, with results not yet published.

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Mode of action still incompletely understood

As of yet, the exact mode of action of BC-007 is still incompletely understood. A better understanding may also answer the question if this aptamere may be a plausible candidate as a treatment for ME/CFS.

Apparently, the infusion of BC-007 is associated with a rapid drop of certain defined GPCR-aabs, incl. aabs targeting ß2-adrenergic receptors (ß2-AAb), Angiontensin-1 receptor (AT-1-AAb), α1-adrenergic receptor (α1-AAb), MAS receptor (MAS-AAb), and muscarinic2-receptor (M2-AAb). A substantial decrease of aab-levels was already measured 2 hours after the beginning of the infusion, and after 2 days no functional activity was observed for any of the aabs measured; seronegativity then continued throughout the observation period of 4 weeks and beyond. Partial symptom improvement has been reported to start already during the 75-minute infusion but this is based on subjective report only. Vascular perfusion as objectively measured by ocular angiography was improved shortly after the infusion and continued to improve for 1-2 days.[3]

So there are at least two open questions around BC-007:

a) how does the drug work?

b) may it be a candidate for treatment of ME/CFS?

Here I want to comment from my own understanding of the background of LC and ME/CFS. [8]

Mode of action of BC-007?

For an answer to this question we may need to consider several remarkable features that have been part of the reports of the experimental trials of BC-007. For one, the (subjective) symptomatology in the treated patient apparently starts to partially improve within a very short time period (within an hour, details, see above). Second: the initial (again: subjective) clinical improvement appears to be in step with both changes in the aab-levels measured and with the improvements in microcirculation measured. Third, aab levels began to drop during the infusion and remained low/undetectable during the whole observation period (an effect which the inventors of BC-007 had already observed for beta-1 aabs in human experiments with BC-007).[9] Fourth, subjective improvement (including a possibly full resolution of symptoms in one patient) seems to last up to several months.

The congruent timeline of symptom improvement and decrease of GPCR-aabs may suggest that symptom resolution may be causally related to the drop of the specific aab-levels measured. This is also plausible because a similar effect – long lasting persistence of autoantibody absence after a one-time removal - has been observed after immunoadsorption in beta-1-adrenoceptor aab positive transplant candidates with dilated cardiomyopathy.[10]

Autoantibody removal may not be the only mode of action

However, while this is plausible, changes in other (as of yet unidentified) aabs or antigens or other mechanisms may play a role and may still need to be considered. (As to the “as of yet unidentified”: A map of possible autoantigens related to SARS-CoV-2 infection comprises of over hundred auto-antigens, including aabs against ACE-2 and angiotensin II – all these aabs may or may not at the same time be targets of BC-007.[11]–[13] [14] Also, antiphospholipid antibodies could develop during a Covid-19 infection and cause antiphospholipid syndrome (APS), an entity widely overlapping with

POTS (and thus possibly worthwhile to be ruled out as possible targets in the BC-007 or similar "pheresis" trials). [15]

As already mentioned, BC-007 also binds to certain SARS-CoV-2 antigens, so its effect could theoretically depend on scavenging SARS-CoV-2 components.[16] This may not be a trivial property of the aptamere as there are indications that some of the lingering effects of SARS-CoV-2 may be related to persistent changes in immune functions [17], [18] or even changes in the function of the ACE-2 receptor.[19]

However, based on the published data and the apparent rapid improvement of microcirculation measured by angiography, the most likely mode of action of BC-007 may indeed be its ability to scavenge pathologically elevated specific GPCR aabs with vasoactive properties (among others, see below). At least the initial clinical improvement reported may plausibly be related to increased perfusion in all vascular regions of the body, including in the brain. This assumption would also fit well with older experiments in ME/CFS patients during a head tilt table test in which an infusion of phenylephrine (epinephrine) rapidly improved neurocognitive function.[20] The latter – unfortunately only short lived - effect has been explained through a phenylephrine-triggered loading of the baroreflex with increase in arterial perfusion pressure and decreased hyperventilation and thus better cerebral blood flow and brain function. The assumption of better cerebral blood flow would also fit with a recent case report of rapid improvement of LC symptoms in 2 patients after a one time stellate ganglion block – an effect that the authors also explain by increased brain perfusion.[21]

The hypothesis that BC-007 *directly* improves microcirculation would also fit well with the findings of an indeed dysfunctional cerebral perfusion and/or autoregulation in both LC an ME/CFS patients (as a matter of fact, in ME/CFS this is the most consistent of all findings: ALL ME/CFS patients examined to this avail so far have been shown to have abnormal cerebral perfusion).[22]–[24]

But how can the lasting effect be explained?

However, this leaves two questions open: How does all this relate to the inflammatory/immune matrix clearly associated with LC (and ME/CFS)? And: how can the long-lasting therapeutic success of a one-time infusion of BC-007 be explained? After all, it is implausible that BC-007 also provides for apoptosis of the aab-producing B-cells – there is just no mechanism to explain this.

More plausibly, the lasting effect of BC-007 may be related to an additional effect on the inflammatory matrix of LC (which may possibly extend to the CNS):

For one, the improved perfusion could induce a virtuous circle by abolishing the „drivers" of inflammation like tissue hypoxia and the associated mitochondrial dysfunction, but also by possibly decreasing the disruption of the blood brain barrier (BBB), which has been shown to maintain neuroinflammation through a constant influx of albumin, fibrinogen and immune cells.[25] The enhanced cerebral perfusion may thus not only cause rapid improvement of brain function through better tissue perfusion but may also abolish the inflammatory milieu which may be at the root of the clonal B-cell expansion and aab-production. The lasting effect of BC-007 may thus reflect the disruption of the vicious circle underlying LC (immune stimulation → inflammation → hypoperfusion → inflammation).

As an alternative (or additional) effect, the improved cerebral perfusion could lead to the abolition of the sympathetic hyperstimulation typical for LongCovid, POTS and ME/CFS. Decreased sympathetic outflow would indeed contribute to normalize the inflammatory milieu in the brain and in the

periphery as sympathetic hyperstimulation has been shown to cause and sustain a pro-inflammatory immune milieu. This hypothesis would again fit well with recent reports of successful treatment of LongCovid by stellate ganglion block which may also work by reducing adrenergic hypertrstimulation.[21]

A third plausible mechanism starts from two of the GPCR-aabs scavenged by BC-007, the AT1 and MAS receptor aabs. The AngII/AT1R axis may indeed play a pivotal role in the pathogenesis of LC (and also ME/CFS) and may in part sustain one of the hallmarks of LC and ME/CFS, i.e. the dysregulated cerebral perfusion (with all its consequences). It has been suggested that the cerebral perfusion defect seen in ME/CFS and LC may be related to a blunted baroreflex, which in turn may be a reflection of AT1/MAS receptor dysfunction.[22], [26]–[28] The latter may also be associated with increased angiotensin II levels – as suspected for ME/CFS and proven in Postural Orthostatic Tachycardia Syndrome (POTS).[29], [30] The increased angiotensin II levels in turn may go along with sympathetic stimulation through epinephrine release, reduced blood flow to the brain, oxidative stress, but also with regulatory CNS dysfunctions, blood brain barrier dysfunction, and, possibly, neuroinflammation – all features that have been implicated in the pathogenesis of LC and ME/CFS.[31]–[33] In this hypothetical explanation of the mode of action of BC-007, this aptamere would restore a functioning AngII/AT1R axis by scavenging AT1/MAS aabs, and thus restore the baroreflex and cerebral autoregulation/perfusion to full function. (To pursue this hypothesis further, it would be interesting to measure angiotensin II and its precursors during and after infusion of BC-007).

Here it may also be important to understand that the AngII/AT1R axis is an important regulatory circuit within the brain („b-RAS“) which is directly and indirectly involved in autonomous and cardiovascular regulation, vigilance and immune signalling (indeed, Ang II also serves as a neurotransmitter). Any effects of BC-007 on AT1/MAS receptor function may therefore have profound reverberations on CNS function which may in part be independent of effects on the microcirculation.

The same argument may apply to another GPCR possibly rendered dysfunctional by aabs in Long Covid (and ME/CFS), namely the endothelin 1 (ET1) B receptor group which has also been shown to have regulatory functions spanning the microcirculation *and* CNS regulation.[34]

Also, it needs to be kept in mind that the majority of adrenergic receptors are expressed in the brain (especially in the brain regions involved in autonomic activity and regulation) and that muscarinergic and adrenergic receptors indeed span a wide range of effector and regulatory functions in the brain, including memory, attention, motor control, sleep-wake-regulation but also memory and cognition. So it may be premature to relate the effects of the removal of adrenergic aabs to effects on the vasculature *alone. (*Here, of course, it may be argued that aabs do not readily cross the BBB, however, this a) does not preclude autoimmunity to happen within the CNS / the innate immune system of the brain and b) this may not apply to an inflammatory CNS milieu, in which the blood-brain barrier is partially dysfunctional. Also, some areas of the CNS are normally devoid of a BBB, such as the circumventricular organs mediating communication between the hypothalamus and brainstem.

… and some more possibilites

There may be even more venues through which BC-007 may achieve its sustained effects, and they also affect the immune/inflammatory matrix of Long Covid:

For one, BC-007 apparently is not only a scavenger of biomolecules, it is also a direct immune modulator. In fact, the inventors of BC-007 consider BC-007 an inhibitor of the toll like receptor 9 (TLR9) and have filed a patent application for this property.[35] TLR9 is an important receptor expressed in immune cells including macrophages and natural killer cells, but also in mast cells and mediates inflammatory responses after both infectious and sterile injury and can in fact be considered a key determinant of the innate immune responses.[36] This involves modulation of inflammatory responses in the CNS. Indeed, TLR9 has been shown to be a key player in neuroinflammation.[37], [38] The receptor has been shown to have a regulatory role in autoimmune diseases, indeed TLR9 antagonists are being developed by the pharmaceutical industry for the treatment of autoimmune diseases. Possibly, and even more of interest to the mode of action of BC-007 may be the fact that TLR9 has been shown to be indispensable in the autoantibody production in B cells in mouse studies.[39]–[41] Therefore, it may be plausible that the inhibiting effect of BC-007 on antibody production may also relate to its effects via TLR9 (here, however, it may again need to be explained why these should persist for months – here again this may hinge on secondary changes like changes in the inflammatory milieu which may drive the clonal expansion of B-cells).

Also, it has to be kept in mind that BC-007 may possibly remove certain inflammatory cytokines. In trials of INUSpheresis, for example, it has been shown that RANTES (CCL5) was removed along aabs[7] (CCL5 has been suggested as a pivotal cytokine in Long Covid).[18] This may not be a trivial process as pro-inflammatory cytokines are linked to the the function of beta-2 receptors in a vicious-cycle dynamic: pro-inflammatory cytokines have been shown to decrease the sensitivity of β-adrenergic receptors; at the same time, chronic activation of β-adrenergic receptors has been shown to induce a pro-inflammatory response with increased expression of TNFα, IL-1β and IL-6 (possibly through NFκB dependent mechanisms).[42] Also, it appears that there is active cross-talk between TNFα receptor signaling and several GPCRs including the β-adrenergic receptor.[42] Therefore, removal of pro-inflammatory cytokines could re-establish normal sensitivity of beta-2 receptors and thus again contribute to the normalization of blood flow (and possibly also reduce sympathetic overdrive and thus decrease further production of inflammatory cytokines).

Direct immune effects?

There is yet another possibility how BC-007 may affect the inflammatory milieu. The adrenergic receptor population, together with a large variety of other GPCRs (including PGE receptors, chemokine receptors, CCR5 or purinergic receptors - which all may potentially also be affected from autoimmune dysfunction after Covid-19), also have profound regulatory influence on immune processes both in the innate and the adaptive immune system.[43], [44] In fact, dysregulation of β_2-AR in microglia and in astrocytes, may contribute to neuroinflammation. Therefore, removal of adrenergic aabs may also have significant reverberations on dysfunctional immune processes, including central ones. The inventors of BC-007 themselves have raised the question if „ beta1-autoantibody activated T cells would be able to act as stimulator of the beta1-autoantibody production, similar to the function of other T cell co-stimulatory factors which again include, e.g., TLR9 ligands, sustaining the vicious circle.“[45] They speculate that this could explain the long lasting effects after a one time infusion.

In summary, BC-007 may achieve its long lasting effect not only be normalizing blood flow in general but also by abolishing drivers of inflammation including neuroinflammation and adrenergic hyperstimulation.

Could BC-007 be effective for ME/CFS?

BC-007 appears as a drug with pleiotropic activities. It is a scavenger of biomolecules, which may have significant direct effects on vascular and immune function. BC-007 additionally may have immune-modulatory properties and have indirect effects on the immune system. A broad mixture indeed: BC-007 may have microcirculatory , immune-modulatory and anti-inflammatory properties (not to forget the anti-coagulation effect for which the aptamere was originally developed).

What does all this mean for ME/CFS? If a similar constellation of aabs is to be found in ME/CFS as in the Long Covid patients treated with BC-007 so far, the patients may benefit from BC-007 to some – as of yet unforeseeable - extent (which may range from small to large improvements from several to regularly repeated infusions). It has indeed been assumed that similar aabs are to be found in about a third of ME/CFS patients (this ratio may actually be higher as the bioassay used by Berlin Cures may be more sensitive than the ELISA used in former studies). The same would apply to POTS in which a similar set of aabs has been recognized as part of the pathophysiological matrix.

As always, it will all come down to further research.

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