Patient Diet may be Critical to your Clinical Trial

Abstract
In designing clinical trials, a great deal of attention is paid to use of other drugs in patient selection. Recent evidence we have uncovered using Qinsight™ suggests patient diet may need to be a carefully controlled. These findings also have implications for safety of drugs already on the market.

Mongersen (SMAD7 inhibitor)
Mongersen, a drug candidate for inflammatory bowel disease, is an inhibitor of SMAD7. This drug failed in a Phase 3 clinical trial\textsuperscript{1}. In an earlier whitepaper, we showed how Qinsight found that statins upregulate SMAD7 and might confound the action of mongersen. In addition, in a query for “What chemicals regulate BCL2?”, we found that there are other compounds that may also interfere with the inhibition of SMAD7.

- **Melatonin** – a common nutraceutical sold over-the-counter. In some reports, melatonin was shown to increase SMAD7\textsuperscript{2,3} potentially counteracting the mongersen-induced decrease. Interestingly, in granulosa cells, melatonin stimulates expression of SMAD6 but not SMAD7\textsuperscript{4,5}.
- **Epigallocatechin gallate** – Green tea is a very popular drink touted widely\textsuperscript{6} as a “healthy beverage” with antioxidants. The most potent compound in green tea is epigallocatechin gallate (EGCG). ECGC enhances expression of SMAD7\textsuperscript{7,8} and hence may also counter the effect of mongersen.

In both of these cases, the compounds are taken orally (as is mongersen) are readily available to the gut.

Ventoclax (BCL2 inhibitor)
Ventoclax, a BCL2 inhibitor, has been approved for the treatment of chronic lymphocytic leukemia. However, a recent Phase 3 trial investigating the use of ventoclax for multiple myeloma was suspended due to safety issues\textsuperscript{9}. With the lessons we learned for mongersen, we queried Qinsight (What chemicals regulate BCL2?) to see if there are similar dietary issues that could have confounded the multiple myeloma trial – or which might suggest possible safety issues in general for ventoclax.

- **Curcumin** – is a component of the spice turmeric and, as a popular health food\textsuperscript{10} is sold as an herbal supplement (pure curcumin or turmeric extract). There is substantial literature on curcumin downregulating expression of BCL2\textsuperscript{6,11,12} possibly potentiating the effect of ventoclax.
- **Resveratrol** – is another stilbenoid compound with substantial hype regarding health benefits\textsuperscript{13} and being sold as a supplement. Plus, this natural polyphenol is found in red wine, blueberries and other foods. Like curcumin, resveratrol has been shown in numerous papers to inhibit BCL2\textsuperscript{e.g.,14,15}.
- **Melatonin** – once again, melatonin may be a confounder for ventoclax treatment as well as mongersen. In some systems, melatonin reduces BCL2 expression\textsuperscript{e.g.,16}. However, in other systems, melatonin was reported to increase BCL2 levels\textsuperscript{e.g.,17}. 
Also of note, but not directly dietary, hormones including estrogen (up-regulation\textsuperscript{18}), estradiol (up-regulation\textsuperscript{19}), androgen (down-regulation\textsuperscript{20}), and progesterone (down-regulation\textsuperscript{21}) alter BCL2 expression.

Selonsertib (MAP3K5 inhibitor)
Selonsertib is a candidate drug for nonalcoholic steatohepatitis. This drug is an MAP3K5 inhibitor that recently failed in a Phase 3 trial\textsuperscript{22}. A query in Qinsight for “What biological processes are connected to MAP3K5” shows the greatest connection to apoptosis – consistent with this gene’s alternate name Apoptosis Signal-regulating Kinase 1 (ASK1), as well as immunity, cell cycle regulation, autophagy, and many other processes. We then investigated what chemicals modulate MAP3K5. As with the drug targets above, there are several articles that link the regulation of MAP3K5 to compounds common in our diets.

- **Glucose** – up-regulates the expression\textsuperscript{23} of MAP3K5 as well as its degree of phosphorylation\textsuperscript{24}. There are, of course, many factors that can alter blood glucose levels besides diet – all of which might therefore affect MAP3K5 activity.
- **Resveratrol** – activates MAP3K5\textsuperscript{25} and could modulate the effect of selonsertib.
- **Epigallocatechin gallate** – reduces phosphorylation of MAS3K5, which is required for the protein’s activation. As such, drinking green tea could potentiate the effect of selonsertib.

Also note that as modulators of apoptosis, curcumin and melatonin (BCL2 inhibitors noted for ventoclax) may also alter response to selonsertib.

Rapastinel (NMDA receptor inhibitor)
Rapastinel is an anti-depressant that was under investigation as a treatment for major depressive disorder. It recently failed in three Phase 3 studies\textsuperscript{26}. Rapastinel enhances NMDA receptor function\textsuperscript{27}. Looking at potential dietary impacts on NMDA receptor activity, we found:

- **Alcohol** – a well-known modulator of NMDA receptors
- **Caffeine** – has also been shown to alter NMDA receptor activity, through up-regulation of the GRIN2 subunit.

In addition, nicotine modifies NMDA receptor activity\textsuperscript{28}, so smoking would be another potential confounder in a study. Hormones also can alter NMDA receptor activity.

Indole Dioxygenase (IDO) Inhibitors
As a class, these potential drugs – including epacadostat, indoximod, and BMS-986205 – have not lived up to expectations\textsuperscript{29}. Once again, common compound in food may modify the activity of indole dioxygenases (IDO1 and IDO2), confounding the results of clinical trials.

- **Epigallocatechin gallate** – Again, ECGC has been found to modify expression of a drug target. In this case, ECGC suppresses IDO expression\textsuperscript{30}.
- **Curcumin** – IDO expression is also suppressed by curcumin\textsuperscript{31}.
- **Resveratrol** – enhanced IDO activity in one study\textsuperscript{32} and inhibited interferon-γ induction of IDO in another study\textsuperscript{33}.

Furthermore, as with BCL2, the hormones estrogen and progesterone stimulate expression of IDO1\textsuperscript{34} and IDO2\textsuperscript{35}. 
Summary

This sampling of the literature, possible through Qinsight's ability to find all compounds of relevance in context, shows there are many instances where clinical trials could be complicated by what the trial participants eat. The recurrence of specific compounds like ECGC and resveratrol in the sections above likely represents the level of interest in these botanical-origin compounds. But, taken as a whole, these findings suggest that what patients ingest during a trial might need to be well-controlled.

The extension of these observations to approved drugs is also likely to be important. Perhaps what patients eat might contribute to those cases where approved drugs were later found to have safety issues.

References

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