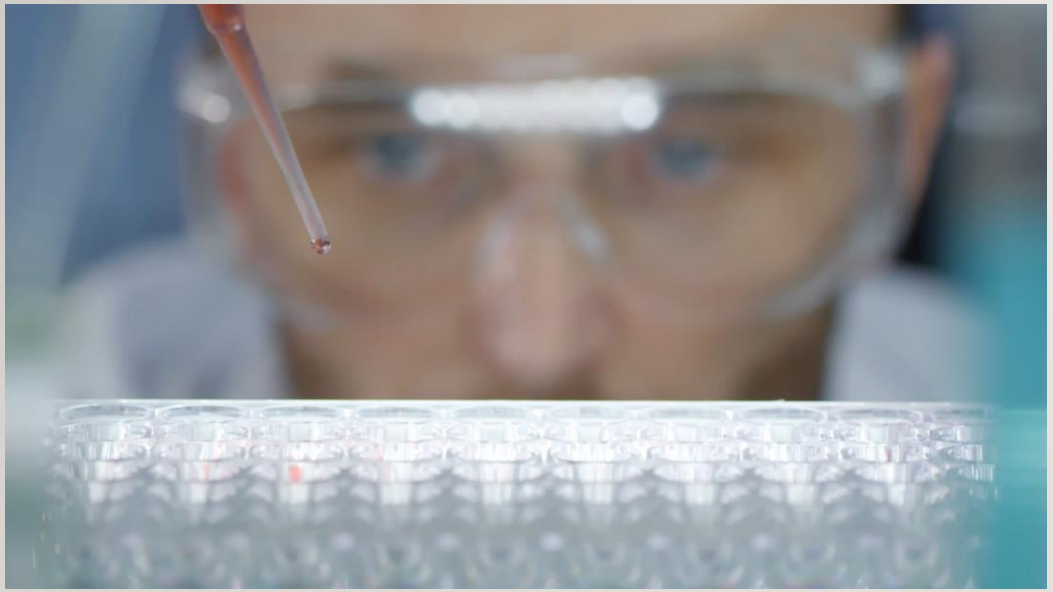

ISOTRETINOIN

WHEN SHOULD WE BE MONITORING?

IS ROUTINE LABORATORY TESTING IN HEALTHY YOUNG PATIENTS TAKING ISOTRETINOIN NECESSARY: A CRITICALLY APPRAISED TOPIC

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WHY DOES IT MATTER?

"It is estimated that 28% of blood tests are taken inappropriately, which comes at a significant cost to patients and healthcare systems. Phlebotomy is both invasive and painful to patients and, in addition to this, medical complications can arise due to excess blood taking, including hospital-acquired / phlebotomy-induced anaemia and infection in an inpatient population who are often already anaemic and immunocompromised. It is estimated that for every 80 mL of blood drawn, haemoglobin levels can fall by 1.0 g/dL. This is associated with increased need for blood transfusions (plus transfusion-associated risks), increased length of stay and increased mortality."

Fisher A, Katumba A, Musa K, et al. Reducing inappropriate blood testing in haematology inpatients: A multicentre quality improvement project. Clin Med (Lond). 2021;21(2):142-146. doi:10.7861/clinmed.2020-0250

WHY DOES IT MATTER?

- Venesection is not free of harm – just ask anyone who has tried to get hospital parking to attend for it!
- It can lead to over-investigation, needless delays in treatment and iatrogenic injury.
- Isotretinoin is a fantastic drug, it can immeasurably improve a patient's quality of life and confidence at a key stage of life.
- We can inappropriately limit patients access to it based on blood testing that is often unnecessary.
- When things do go wrong, the blood tests can be falsely reassuring.

AIMS

- To evaluate whether the following routine blood testing for isotretinoin is needed in healthy patients:
  - liver function
  - full blood count
  - thyroid function tests
  - muscle enzymes
- Triglyceride abnormalities due to isotretinoin were the subject of a 2016 review by Opel et al, which followed the format and methodology of a CAT.

Opel D, Kramer ON, Chevalier M et al. Not every patient needs triglyceride check, but all can get pancreatitis: A systematic review and clinical characterization of Isotretinoin associated Pancreatitis. Br J Dermatol 2016.

METHODOLOGY

- We chose the blood tests based on discussion, package inserts and BAD guidelines.
- We performed four individual systematic searches of MEDLINE, via PUBMED, databases from origin to May 2, 2021, supplemented by a hand search of all references in identified papers.
- Inclusion criteria were:
  - Any description of clinical symptoms, laboratory abnormalities and/or adverse physical findings related to isotretinoin.
  - Any paper that explicitly described the patients as asymptomatic, during treatment with oral isotretinoin.

METHODOLOGY

- Relevant papers were independently selected for review by Dr Albrecht and Dr Jackson.
- A predetermined data form was used to extract information that included study design, sample size, and events with conclusions reported in the article.

Study type	N – studies	N - patients
Liver		
Case reports	9	9
Cohort studies - prospective	8	1408
Cohort studies – unclear or retrospective	28	23358
RCTs	6	397
Review or meta-analysis	10	NA
Thyroid		
Case reports	6	6
Cohort studies - prospective	6	233
Hematology		
Case reports	10	10
Cohort studies – prospective	4	302
Cohort studies – unclear or retrospective	6	17074
Review or meta-analysis	1	NA
Muscle		
Case reports	14	15
Cohort studies - prospective	1	89
Cohort studies – unclear or retrospective	4	1076
Review or meta-analysis	3	NA

TOXICOLOGICAL APPROACH

- Analysis of rare events has to be clinical since statistical methods are not useful for exceedingly rare events.
- As a consequence case reports remain the basis for a majority of safety decisions by regulatory agencies, such as the FDA.
- Drugs are removed from the market when the incidence of drug induced liver injury (DILI) rises above 1 in 10.000.
- Based on the 'rule of three', a series of about 30.000 patients without event would be needed to show that the risk of DILI is below 1 in 10.000.

Table 1.—Probability That a Sample of 167 Will Have No Complications

If Long-Run Complication Rate is...	Probability (%) of Observing 0 Complications in 167 is...
1 in 10,000	98
1 in 1000	85
1.5 in 1000	78
1 in 200	43
1 in 100	19
1 in 56	5
1 in 25	0.1

Table 2.—Long-Run Risk "Ruled Out" by 0/ n

(With 95% Confidence, ie, 5% Limit of Credibility)

Observed Rate of...	Rules Out Any Long-Run Rate (%) Higher Than
0/10	26* (30)†
0/20	14 (15)
0/30	10 (10)
0/50	6 (6)
0/100	3 (3)
0/1,000	0.3 (0.3)

*$(1-\text{maximum rate})^n = 0.05$

†Derived from rule of three.

Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA 1983; 249: 1743-5.

LIVER INJURY

Study type	N – studies	N - patients
Liver		
Case reports	9	9
Cohort studies - prospective	8	1408
Cohort studies – unclear or retrospective	28	23358
RCTs	6	397
Review or meta-analysis	10	NA

Total 25,172 patients

LIVER INJURY

- Isotretinoin leads to a transient elevation of liver enzymes in a large proportion of patients – in the vast majority of cases this normalises without cessation of the drug.
- We identified only one poorly documented case of "probable" DILI (based on the Council for the international organization of medical sciences/Roussel Uclaf Causality Assessment Method).
- One report linked autoimmune hepatitis in a patient with Hashimoto thyroiditis to isotretinoin after 3 months of therapy. The authors failed to recognize the association of Hashimoto thyroiditis with autoimmune hepatitis (4 of 46 patients with Hashimoto thyroiditis had autoimmune hepatitis in one series).
- A third patient developed mild derangement of liver enzymes on isotretinoin. After four months of therapy a biopsy found hepatosteatosis. Assessing causation is difficult, since hepatosteatosis is frequently found on biopsy of asymptomatic patients with liver enzyme elevation.

LIVER INJURY

- Since it's approval in 1982, we found one case of probable DILI reported. One case of hepatitis in a patient with a background of Hashimoto's and one case of unexplained steatohepatitis in a patient taking isotretinoin.
- In the UK no death due to hepatobiliary disorders have ever been reported secondary to isotretinoin via the yellow card system (vs 21 for trimethoprim and 4 for doxycycline).
- Isotretinoin can be used in patients who have experienced liver injury due to etretinate and acitretin.
- It should be noted that asymptomatic DILI, even if it crosses the threshold of laboratory diagnosis, may resolve on continuing therapy.

McElwee NE, Schumacher MC, Johnson SC et al. An observational study of isotretinoin recipients treated for acne in a health maintenance organization. Arch Dermatol 1991; 127: 341-6.

LIVER INJURY - CONCLUSIONS

- The incidence of isotretinoin induced DILI is exceedingly rare.
- Given the available data, we suspect that isotretinoin behaves similarly to other drugs like aspirin and heparin, that increase liver enzymes without causing DILI.
- Blood tests will find transient elevations that may be irrelevant but need further work up.
- The level of abnormality is not necessarily a guide to clinical significance.
- The evidence we reviewed does not suggest that monitoring is helpful, particularly in younger healthy patients.

FBC MONITORING

Study type	N – studies	N - patients
Hematology		
Case reports	10	10
Cohort studies – prospective	4	302
Cohort studies – unclear or retrospective	6	17074
Review or meta-analysis	1	NA

Total 17386 patients

FBC MONITORING

- Mild haematological abnormalities are common in patients on isotretinoin.
- No deaths due to haematological disorders have been reported via yellow card in the UK for isotretinoin.
- Based on case reports, we identified two probable cases of isotretinoin induced neutropenia, and two of thrombocytopenia.
- Isotretinoin was not identified in a multi-national study of drug-induced agranulocytosis and is not considered a drug of high risk.
- It is likely that the risk of agranulocytosis is lower than the 0.6 cases per 106 users/week that was found for doxycycline.
- To evaluate such rare events, one would likely need a cohort study sized in the 100,000s for stable estimates.

FBC MONITORING - CONCLUSIONS

- Given this degree of rarity, routine monitoring is no longer recommended by either the BNF or EMC4.
- However, given sepsis develops rapidly in the setting of agranulocytosis it may be prudent to warn patients of symptoms of blood dyscrasias (e.g. sore throat, fever, severe malaise) rather than to monitor bloods at monthly intervals.
- For Dapsone, even weekly monitoring has been insufficient to prevent lethal agranulocytosis-induced sepsis in some patients.

THYROID DYSFUNCTION

Study type	N – studies	N - patients
Thyroid		
Case reports	6	6
Cohort studies - prospective	6	233

THYROID DYSFUNCTION

- Thyroid abnormalities secondary to isotretinoin have been reported since the 1980's but the number of cases is small, and no pattern of timeline or abnormalities has emerged to support causation.
- Prospective cohort studies have followed isotretinoin patients to investigate the influence of isotretinoin on hormonal homeostasis. Some of these studies found mild changes of thyroid hormones, but none were clinically significant.
- National guidelines in the US and the UK do not recommend screening for thyroid disease in asymptomatic patients.
- 19 cases of unspecified endocrine disorders have been reported in the UK, none lethal.
- In summary, thyroid test screening in patients on isotretinoin is likely unnecessary in the asymptomatic.

MUSCLE

Study type	N – studies	N - patients
Muscle		
Case reports	14	15
Cohort studies - prospective	1	89
Cohort studies – unclear or retrospective	4	1076
Review or meta-analysis	3	NA

Total 1180 patients

MUSCLE

- Myalgia and mild transient elevations in CK are common, and were observed in 20% of patients in a small series.
- Significant elevations are much less frequent, with CK >5 x upper reference range in 1.2% - 1.6%
- Transient elevations of CK with exercise are common in young fit individuals, with levels as high as 35056 IU/L in healthy training military recruits.
- In young healthy patients, even relatively high CK levels (>5xupper reference range) are unlikely to precipitate rhabdomyolysis.
- It should also be noted that elevations in CK do not always correlate with symptoms of myalgia and severe myalgia with significant proximal weakness/stiffness has been reported with minimal change in CK levels.
- Our literature review identified 8 cases of rhabdomyolysis secondary to isotretinoin, with one fatality.
- This has occurred with as little as 20mg daily dosing, though cases often note recent vigorous exercise as a potential trigger.

MUSCLE - CONCLUSIONS

- Whilst the incidence of rhabdomyolysis is unknown, given the paucity of case reports, it is likely to be rare.
- In the UK about 500 cases of musculoskeletal disorders have been reported since 1983, that is about 12 per year, though none of them lethal.
- If these cases are rapidly precipitated by vigorous exercise, routine CK monitoring is likely ineffective.
- Education regarding limiting vigorous physical activity and identifying clinical symptoms of rhabdomyolysis (fatigue, myalgia and myoglobinuria) are likely a more effective strategy.
- For statin therapy, rhabdomyolysis is a significant problem. The lipid expert panel has developed algorithms for athletes that suggest therapy breaks, dose adjustment, or therapy changes based on CK results. These cannot be applied directly to isotretinoin, but the approach may be helpful in select cases.

ISOTRETINOIN ASSOCIATED PANCREATITIS

- Triglyceride abnormalities due to isotretinoin were the subject of a 2016 review by Opel et al, which followed the format and methodology of a CAT.

Opel D, Kramer ON, Chevalier M et al. Not every patient needs triglyceride check, but all can get pancreatitis: A systematic review and clinical characterization of Isotretinoin associated Pancreatitis. Br J Dermatol 2016.

ISOTRETINOIN ASSOCIATED PANCREATITIS

- Isotretinoin has been shown to reliably increase triglyceride levels by 20-40% and reduce high density lipids. Due to the brevity of treatment this is unlikely to increase cardiovascular risk.
- Hypertriglyceride-associated pancreatitis is an exceedingly rare adverse event with isotretinoin, which is now thought not to occur in patients with fasting triglycerides <2000mg/dL (22.6mmol/l).
- Triglyceride-induced pancreatitis has been reported in three patients who were older than 35 years and had elevated triglycerides at baseline. There are no reports of this in younger patients.

Opel D, Kramer ON, Chevalier M et al. Not every patient needs triglyceride check, but all can get pancreatitis: A systematic review and clinical characterization of Isotretinoin associated Pancreatitis. Br J Dermatol 2016.

ISOTRETINOIN ASSOCIATED PANCREATITIS

- Idiosyncratic pancreatitis, without hypertriglyceridemia, due to isotretinoin is a very rare but real adverse event and can occur in young patients.
- It is poorly understood, but more frequent than hypertriglyceridemia associated pancreatitis.
- Triglyceride monitoring is unlikely to be helpful at preventing these cases, and education regarding symptoms of pancreatitis may be a more appropriate intervention.

Opel D, Kramer ON, Chevalier M et al. Not every patient needs triglyceride check, but all can get pancreatitis: A systematic review and clinical characterization of Isotretinoin associated Pancreatitis. Br J Dermatol 2016.

ISOTRETINOIN ASSOCIATED PANCREATITIS

- It is appropriate to check triglycerides at baseline, and 6-8 weeks, in those who have risk factors for elevated triglycerides (truncal obesity, family history, signs of insulin resistance).
- Monitoring thereafter is unlikely to be helpful unless there is dose adjustment.
- In those without risk factors, triglyceride monitoring may not be helpful, and advice regarding symptoms of pancreatitis may be a more appropriate intervention.

CONCLUSIONS

- Our review used published data of adverse events and thus will only identify a small subset of cases that have occurred.
- It has been estimated that the yellow card system only identifies 10% of all serious adverse events.
- Nevertheless, isotretinoin has been on the market for nearly 40 years and based on usage data from 2013-2019 we estimate that isotretinoin has been prescribed in the US alone to at least 10.000.000 patients.
- In the UK, none of the organ systems discussed have been associated with death by the yellow card system, unlike for drugs such as trimethoprim and doxycycline.
- Whilst none of the cohort studies included were powered to identify very rare adverse events (this is just not feasible), given the number of papers and cohort studies we are optimistic that the range and rarity of adverse events that we identified is representative.

CONCLUSIONS

- Our review could not identify a single blood test that seems reasonable to perform routinely, given the rarity of the adverse outcomes identified in the literature in healthy young patients, or the rapidity of their clinical development.
- Rather than routine, we believe that blood tests need to be individualized based on risk factors. Patients with significant obesity, acanthosis nigricans, diabetes, or history of significant hypertriglyceridemia may benefit from baseline triglycerides, but the overwhelming majority will never reach the fasting 2000mg/dL-1 that put them at risk for pancreatitis.
- Liver function tests will frequently be elevated on isotretinoin but the risk of DILI is negligible, if it even exists, and routine monitoring is not helpful. Minor cell death is part of liver adaptation to various drugs.
- Patients need to be informed about isotretinoin's rare adverse events, particularly pancreatitis and rhabdomyolysis, so they are aware to present should symptoms develop.
- However, routine monitoring may be falsely reassuring without improving safety. It likely drives over-investigation of spurious results, generating avoidable healthcare costs and causes confusion and anxiety until results are correctly evaluated.
- It should also be noted that the adverse events we identified in this review are considered so irrelevant that regulatory agencies have not found it necessary to react with package insert amendments, or black box warnings. We agree with that assessment.